EXHIBIT C

United States Patent **7,371,367**
Bernstein **May 13, 2008**

Method of treating inflammatory acne vulgaris and rosacea with carbamide peroxide

Abstract

A method of treating inflammatory acne vulgaris or inflammatory acne rosacea comprises the topical application of a formulation incorporating carbamide peroxide in a pharmaceutically acceptable vehicle. Inflammatory acneform lesions that can be successfully treat with the inventive method include erythematous papules, pustules, nodules, and cysts. Suitable pharmaceutical vehicles for the topical application of carbamide peroxide include creams, gels, lotions, solutions, suspensions, and ointments.

Inventors: ***Bernstein*; Joel E.** (Deerfield, IL)
Assignee: **Exopharma, Inc.** (Vernon Hills, IL)
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Field of Search: 514/24,554,588 424/70.13,70.16,70.31

References Cited [Referenced By]

U.S. Patent Documents

4607101	August 1986	Bernstein
2004/0220264	November 2004	Yu et al.

Primary Examiner: ***Marschel***; Ardin
Assistant Examiner: Vakili; Zohreh
Attorney, Agent or Firm: Barnes & Thornburg, LLP Martin; Alice O.

Claims

What is claimed is:

1. A method of treating inflammatory acne rosacea in patients having inflammatory acneform lesions of rosacea comprising administering a therapeutically effective amount of carbamide peroxide in a vehicle suitable for topical application to the skin to a pateint with such lesions.

2. The method of claim 1 wherein the carbamide peroxide is present in the amount of about 1.0% to about 15.0% by weight.

3. The method of claim 1 wherein said vehicle is selected from the group consisting of solutions, suspensions, creams, ointments, gels and lotions.

Description

BACKGROUND OF THE INVENTION

Acne vulgaris is a disease of the pilosebaceous glands characterized by an unsightly eruption of the skin of the face, neck, back and chest. Acne vulgaris is a common affliction of the adolescent and affects a small but significant percentage of the adult population. Acne vulgaris lesions are of four basic types: comedones (blackheads or whiteheads,) papules, pustules, and cysts (or nodules). Various topical agents used in the treatment of acne vulgaris include sulfur, sulfur compounds, resorcinol, salicylic acid, benzoyl peroxide, various retinoids including tretinoin, tazarotine and adopalene, and topical antibiotics. Acne vulgaris involvement results in unsightly lesions, particularly on the face, and in some cases results in severe scarring.

Acne rosacea, commonly called simply rosacea, is an inflammatory disorder of the skin that, despite its name, seems to bear no relationship to acne vulgaris. In contrast to acne vulgaris, rosacea occurs predominantly in middle-aged adults and is virtually never observed in adolescents or young adults. Rosacea is characterized by inflammatory lesions of the skin that resemble acne vulgaris papules and pustules ("acneform" lesions) and a disorder of the superficial cutaneous vasculature resulting in erythema, accentuated flushing and telangiectasia. Comedones, a hallmark of acne vulgaris, do not occur as part of the rosacea "complex." Rosacea is treated with a variety of topical therapies including sodium sulfacetamide, topical antibiotics and metronidazole.

Carbamide peroxide (also known as urea peroxide) is a chemical long used as an agent to soften earwax for removal and in mouthwashes to provide cleansing action in the oral cavity. In recent years carbamide peroxide has been incorporated into toothpastes for the purpose of whitening teeth. Carbamide peroxide's first use for the treatment of acne vulgaris was disclosed in U.S. Pat. No. 4,607,101 issued Aug. 19, 1986, incorporated herein by reference in its entirety.

U.S. Pat. No. 4,607,101 disclosed a method of treating non-inflammatory acne vulgaris, composed of open and closed comedones, with topically applied carbamide peroxide. In the Examples of U.S. Pat. No. 4,607,101, carbamide peroxide was used to treat open and closed comedones, and carbamide peroxide in combination with either an antibiotic or nicotinamide was used to treat patients having both comedones and inflammatory lesions of acne vulgaris.

The applicant has discovered, quite surprisingly (and in direct opposition to the teaching in U.S. Pat. No. 4,607,101) that carbamide peroxide by itself is quite effective at treating the inflammatory lesions of acne vulgaris, and acne rosacea. The invention, therefore, encompasses an improved method of treating inflammatory acne vulgaris or rosacea utilizing application to the skin of solutions, creams, gels, or lotions containing carbamide peroxide.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the invention, a method of treating inflammatory acne vulgaris and the acneform lesions of rosacea comprises the topical application of formulations that incorporate carbamide peroxide into pharmaceutically acceptable vehicles. Inflammatory acne vulgaris is characterized by the presence of erythematous papules, pustules and cysts.

Suitable pharmaceutical vehicles for applying carbamide peroxide within the scope of the method include creams, gels, lotions, suspensions, ointments, and solutions. The carbamide peroxide can be present in the formulation as about 1.0-15.0% by weight, and preferably about 5.0-10.0% by weight. Methods of preparing such formulations will be readily apparent to and understood by those skilled in the art. The following examples illustrate the present invention.

EXAMPLE 1

Sixty patients with inflammatory acne vulgaris, defined as having acne vulgaris and at least 6 papules and/or pustules on each side of the face, were treated twice daily with a 10% carbamide peroxide solution (containing 86% ethanol, 3% glycerin and 1% citric acid) on one side of the face and its unmedicated vehicle on the other side of the face for eight weeks. At the end of the eight-week treatment period the sides of the face treated with carbamide peroxide showed significantly greater improvement in the inflammatory acne lesions then did the vehicle treated sides.

EXAMPLE 2

A 20-year-old male with inflammatory (papulo-pustular) acne applied a 5% carbamide peroxide gel (containing 91% ethanol, 3% hydroxylpropylcellulose, and 1% citric acid) twice daily to his face. After a twelve week treatment period, the number of inflammatory lesions had been reduced from nine to one.

EXAMPLE 3

A 48-year-old female with rosacea and four acneform papular lesions of the nose and cheeks applied the 10% carbamide peroxide solution of Example 1 to her face three times daily for eight weeks. At the end of the eight weeks her face was clear of rosacea papules.

While the foregoing is a description of preferred embodiments of the invention, it will be readily apparent to those skilled in the art that various modifications may be made therein without departing from the true scope and spirit of the invention as set forth in the following claims.

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United States Patent **7,323,463**
Chang , et al. **January 29, 2008**

Combination of brimonidine and timolol for topical ophthalmic use

Abstract

Disclosed are pharmaceutical compositions comprising brimondine and timolol for topical ophthalmic delivery and a method of treatment comprising administering said composition when indicated for glaucoma and associated conditions such as elevated intraocular pressure in the eyes of humans.

Inventors: **Chang; Chin-Ming** (Tustin, CA), **Beck; Gary J.** (Fullerton, CA), **Pratt; Cynthia C.** (Mission Viejo, CA), **Batoosingh; Amy L.** (Mission Viejo, CA)

Assignee: **Allergan, Inc.** (Irvine, CA)

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Related U.S. Patent Documents

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10126790	Apr., 2002	7030149	

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Field of Search: 514/393,398,399,236.2 424/427

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Primary Examiner: Kwon; Brian
Attorney, Agent or Firm: Johnson; Brent A. Voet; Martin A. Baran; Robert J.

Parent Case Text

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a divisional application under 37 CFR 1.53(b) and 1.78(a), of pending prior parent application Ser. No. 10/126,790, filed on Apr. 19, 2002 for COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE.

Claims

The invention claimed is:

1. A composition comprising about 0.2% timolol by weight and about 0.5% brimonidine by weight as the sole active agents, in a single composition.

2. The composition of claim 1 further comprising from 0.001% to 0.01% benzalkonium chloride.

3. The composition of claim 2 comprising about 0.005% benzalkonium chloride.

4. An article of manufacture comprising packaging material and a composition within said packaging material, wherein said composition comprises about 0.2% timolol by weight and about 0.5% brimonidine by weight, in a single composition, and wherein said packaging indicates that the composition is useful for treating glaucoma or ocular hypertension by twice a day topical administration of the composition to a person's eye.

5. The article of manufacture of claim 4 wherein the composition further comprises from 0.001% to 0.01% benzalkonium chloride.

6. The article of manufacture of claim 5 wherein the composition further comprises about 0.005% benzalkonium chloride.

Description

BACKGROUND OF THE INVENTION

This invention relates to the topical ophthalmic use of brimonidine in combination with timolol when indicated for treatment of glaucoma or ocular hypertension. Such combinations or formulations are available for separate use in the ophthalmic art and have been combined in serial application during the course of treatment of glaucoma. However, there are concerns and expressed reservations in the ophthalmic community about patient compliance when the patient is required to administer separate medications to treat a single disease or condition such as glaucoma. There is, moreover, a long felt need for an effective and safe topical ophthalmic pharmaceutical composition including brimonidine and timolol which has increased stability and requires a lower effective concentration of preservative as compared to the individual agents taken alone. Finally, there is a need to increase the efficacy of many topical ophthalmic agents, without increasing the systemic concentration of such topical agents, since it

is well known that many of such topically-applied ophthalmic agents cause systemic side effects, e.g. drowsiness, heart effects, etc. Unexpectedly it has been discovered that brimonidine in combination with timolol meets these criteria.

Brimonidine is disclosed in U.S. Pat. No. 3,890,319. The use of brimonidine for providing neuroprotection to the eye is disclosed in U.S. Pat. Nos. 5,856,329; 6,194,415 and 6,248,741.

Timolol, as an ophthalmic drug, is disclosed in U.S. Pat. Nos. 4,195,085 and 4,861,760.

DESCRIPTION OF THE INVENTION

Brimonidine is an alpha adrenergic agonist represented by the following formula:

##STR00001##

The chemical name for brimonidine is 5-Bromo-6-(2-imidazolidinylideneamino)quinoxaline L-tartrate.

Timolol is a beta adrenergic agent represented by the following formula:

##STR00002##

Brimonidine is available from Allergan, Inc., Irvine, Calif. as an ophthalmic pharmaceutical product having the name Alphagan.RTM.. Timolol is available from various sources, including Merck Co., Rahway, N.J.

The compositions of the present invention are administered topically. The dosage is 0.001 to 1.0, e.g. mg/per eye BID; wherein the cited mass figures represent the sum of the two components, brimonidine and timolol. The compositions of the present invention can be administered as solutions in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the mixtures are preferably formulated as 0.01 to 0.5 percent by weight brimonidine and 0.1 to 1.0 percent by weight timolol solution in water at a pH of 4.5 to 8.0, e.g. about 6.9. While the precise regimen is left to the discretion of the clinician, it is recommended that the solution be topically applied by placing one drop in each eye two times a day. Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. In the prior art ophthalmic products, typically such preservatives are employed at a level of from 0.004% to 0.02%. In the compositions of the present application the preservative, preferably benzalkonium chloride, may be employed at a level of from 0.001% to less than 0.01%, e.g. from 0.001% to 0.008%, preferably about 0.005% by weight. It has been found that a concentration of benzalkonium chloride of 0.005% is sufficient to preserve the compositions of the present invention from microbial attack. This concentration may be advantageously compared to the requirement of 0.01% benzalkonium chloride to preserve timolol in the individual, commercially-available ophthalmic products. Moreover, it has been found that adequate lowering of intraocular pressure has been obtained when administering the

compositions of this invention twice a day as compared to the FDA-approved regimen wherein brimonidine ophthalmic solution, i.e. Alphagan.RTM. ophthalmic solution is administered three times a day and timolol ophthalmic solution, i.e. Timoptic.RTM. ophthalmic solution is administered twice a day. This results in the exposure of the patient to 67% and 50% of benzalkonium chloride, with the compositions of this invention, as compared to the administration of Alphagan.RTM. and Timoptic.RTM., respectively. In FDA-approved adjunctive therapy, wherein Alphagan.RTM. and Timoptic.RTM. are serially administered, the patient is exposed to almost three times the concentration of benzalkonium chloride as compared to the administration of the compositions of this invention twice a day. (It is noted that it is known that benzalkonium chloride at high concentrations is cytotoxic. Therefore, minimizing the patient's exposure to benzalkonium chloride, while providing the preservative effects afforded by benzalkonium chloride, is clearly desirable.)

Co-Solvents:

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such cosolvents include polysorbate 20, 60, and 80, Pluronic F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents:

Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity building agents include as examples polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The present invention further comprises an article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for lowering intraocular pressure and wherein the packaging material comprises a label which indicates the pharmaceutical agent can be used for lowering intraocular pressure and wherein said pharmaceutical agent comprises an effective amount of brimonidine and an effective amount of timolol.

The following example is a representative pharmaceutical composition of the invention for topical use when indicated for treating glaucoma.

EXAMPLE I

The combination of active pharmaceutical ingredients is as follows: Brimonidine Tartrate 0.20% (w/v) and Timolol Maleate 0.68% (w/v) (Equivalent to 0.50% (w/v) timolol)

The Brimonidine-Timolol combination formulation presented in the Table, below, is a sterile, preserved, aqueous solution. The formulation vehicle is based upon a timolol ophthalmic solution which contains an isotonic phosphate buffer system at pH 6.9. The formulation preservative is benzalalkonium chloride (BAK) at a concentration of 0.005% (w/v) (50 ppm). The formulation passes regulatory required preservative efficacy testing (PET) criteria for USP (United States Pharmacopoeia) and EP (European Pharmacopoeia-A and -B over 24 months.

TABLE-US-00001 TABLE Concentration, Ingredient Function % (w/v) Brimonidine Tartrate Active 0.2 Timolol Maleate, EP Active 0.68.sup.1 Benzalkonium Chloride, NF, EP Preservative 0.005 Sodium Phosphate, monobasic Buffer 0.43 monohydrate, USP Sodium Phosphate, dibasic Buffer 2.15 heptahydrate, USP Sodium Hydroxide, NF pH adjust Adjust pH to 6.9 Hydrochloric Acid, NF pH adjust Adjust pH to 6.9 Purified Water, USP, EP Solvent q.s. ad .sup.1Equivalent to 0.5 % (w/v) Timolol, free base

The pharmaceutical composition of Example I is used in the clinical study reported below.

EXAMPLE II

Objectives:

To compare the safety and efficacy of twice-daily dosed brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution combination (henceforth referred to as Combination) with that of twice-daily dosed timolol ophthalmic solution 0.5% (henceforth referred to as Timolol) and three-times-daily dosed ALPHAGAN.RTM. (brimonidine tartrate ophthalmic solution) 0.2% (henceforth referred to as Brimonidine) administered for three months (plus 9-month masked extension) in patients with glaucoma or ocular hypertension.

Methodology:

Structure: multicenter, double-masked, randomized, parallel-group, active control

Randomization: patients were randomized to one of the 3 masked treatment groups (Combination, Brimonidine or Timolol) based on an even allocation at each site.

Visit Schedule: prestudy, baseline (day 0), week 2, week 6, month 3, month 6, month 9, and month 12.

Number of Patients (Planned and Analyzed):

560 planned to enroll; 586 enrolled (Combination=193, Brimonidine=196, Timolol=197); 502 completed. Mean (range) age: 62.4 (23 to 87) years; 46.1% (270/586) males, 53.9% (316/586) females.

Diagnosis and Main Criteria for Inclusion:

Diagnosis: ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma and requiring bilateral treatment.

Key Inclusion Criteria: .gtoreq.18 years, day 0 (post-washout) intraocular pressure (IOP) .gtoreq.22 mm Hg and .ltoreq.34 mm Hg in each eye and asymmetry of IOP .ltoreq.5 mm Hg, best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.

Key Exclusion Criteria: uncontrolled systemic disease, abnormally low or high blood pressure or pulse rate for age or contraindication to beta-adrenoceptor antagonist therapy, anticipated alteration of existing chronic therapy with agents which could have a substantial effect on IOP, contraindication to brimonidine therapy, allergy or sensitivity to any of the study medication ingredients, anticipated wearing of contact lenses during the study, laser surgery, intraocular filtering surgery or any other ocular surgery within the past 3 months, or required chronic use of other ocular medications during the study

(intermittent use of artificial tear product was allowed).

Test Product, Dose and Mode of Administration, Batch Number:

Brimonidine tartrate 0.2%/timolol 0.5% combination ophthalmic solution one drop (.about.35 .mu.L) instilled in each eye BID in the morning and evening; and vehicle of the Combination ophthalmic solution, one drop (.about.35 .mu.L) instilled in each eye once daily (QD) in the afternoon (for masking purposes).

Duration of Treatment: 3 months (with a 9-month masked extension)

Reference Therapy, Dose and Mode of Administration, Batch Number:

Active control ALPHAGAN.RTM. (brimonidine tartrate ophthalmic solution) 0.2%, one drop (.about.35 .mu.L) instilled in each eye TID in the morning, afternoon, and evening. Active control timolol ophthalmic solution 0.5%, one drop (.about.35 .mu.L) instilled in each eye BID in the morning and evening; and vehicle of the Combination ophthalmic solution, one drop (.about.35 .mu.L) instilled in each eye once daily (QD) in the afternoon (for masking purposes).

Criteria for Evaluation:

Efficacy:

IOP (hours 0, 2, 7, and 9), patient satisfaction questionnaire, patient comfort of study medication questionnaire, pharmacoeconomic evaluation by investigator

Safety:

Adverse events (AE), biomicroscopy, visual acuity (VA), visual field, ophthalmoscopy, cup/disc ratio, heart rate, blood pressure, hematology, serum chemistry, urinalysis and pregnancy test.

Other:

Quantitation of plasma brimonidine and timolol concentrations (at selected sites), resource utilization (to be reported upon completion of the 1 year study).

Statistical Methods:

All data were summarized with descriptive statistics, frequency tables, and/or data listings. Safety analyses included all patients who received at least 1 dose of study medication. Analyses were performed for the primary efficacy variable IOP using the intent-to-treat (ITT) population with last observation carried forward (LOCF), and the per protocol population with observed cases.

Ordinal categorical variables were analyzed by the Wilcoxon rank-sum test. Nominal categorical variables were analyzed using Fisher's exact or Pearson's chi-square tests. Within-group changes from baseline for categorical variables were analyzed using the Wilcoxon signed-rank test. Continuous variables (eg, IOP) were analyzed using analysis of variance (ANOVA). Within-group changes from baseline for continuous variables were analyzed using paired t-tests.

A 2-way ANOVA model with factors for treatment and investigator was used for the analysis of IOP. Comparisons were made between the Combination and each of the 2 monotherapies in a pairwise

fashion using contrasts from the ANOVA model, with the same error term. A separate ANOVA model was employed at each hour/visit measurement of IOP. Each of the 2 null hypotheses (Combination versus Timolol and Combination versus Brimonidine) was tested at the 0.05 significance level. Point estimates of the mean treatment differences, as well as 2-sided 95% confidence intervals (CI) of the difference, were provided at each timepoint.

Summary--Conclusions:

Efficacy:

At baseline, mean values of diurnal IOP ranged from 22.2 mm Hg to 24.9 mm Hg in the Combination group, 22.5 mm Hg to 25.0 mm Hg in the Brimonidine group, and 22.3 mm Hg to 24.8 mm Hg in the Timolol group. There were no statistically significant differences between treatment groups.

Mean changes from baseline diurnal IOP at week 2, week 6 and month 3 ranged from: -5.2 to -7.9 mm Hg in the Combination group -3.5 to -5.7 mm Hg in the Brimonidine group -4.5 to -6.4 mm Hg in the Timolol group

The mean decreases from baseline diurnal IOP were statistically significant within each treatment group at each follow-up timepoint,($p<0.001$).

The mean decrease from baseline diurnal IOP was statistically significantly greater with Combination than with Brimonidine at hours 0, 2, and 7 at all follow-up visits ($p<0.001$). In addition, clinically significant differences of more than 1.5 mm Hg in mean change from baseline IOP favoring Combination over Brimonidine were seen at hours 0, 2, and 7 at all follow-up visits. At hour 9, the decreases from baseline diurnal IOP were greater for the Combination group than the Brimonidine group at all follow-up visits, although the differences were not statistically significant (p.gtoreq.0.104).

The mean decrease from baseline diurnal IOP was statistically significantly greater with Combination than with Timolol at hours 0, 2, 7 and 9 at all follow-up visits (p.ltoreq.0.041). In addition, clinically significant differences of more than 1.5 mm Hg in mean change from baseline IOP favoring Combination over Timolol were seen at week 2 (hours 0, 2, and 7), week 6 (hours 2 and 7), and month 3 (hours 0 and 2). Mean values of diurnal IOP at week 2, week 6 and month 3 ranged from: 15.9 to 18.1 mm Hg in the Combination group 17.4 to 21.5 mm Hg in the Brimonidine group 17.5 to 18.9 mm Hg in the Timolol group

Mean values of diurnal IOP were statistically significantly less with Combination than with Brimonidine at hours 0, 2, and 7 at all follow-up visits ($p<0.001$) and at hour 9 at week 6 and month 3 (p.ltoreq.0.011). The mean values of IOP at hour 9 at week 2 were lower for the Combination group than the Brimonidine group, although the difference was not statistically significant ($p=0.205$). In addition, clinically significant differences of more than 1.5 mm Hg in mean IOP favoring Combination over Brimonidine were seen at hours 0, 2, and 7 at all follow-up visits and at hour 9 at month 3.

Mean values of diurnal IOP were statistically significantly less with Combination than with Timolol at hour 0 at week 2 and month 3; and at hours 2, 7 and 9 at all follow-up visits (p.ltoreq.0.050). The mean values of IOP at hour 0, week 6, were lower for the Combination group than the Timolol group, although the difference was not statistically significant ($p=0.102$). In addition, clinically significant differences of more than 1.5 mm Hg in mean IOP favoring Combination over Timolol were seen at week 2 (hours 0, 2, and 7), week 6 (hours 2, 7, and 9), and month 3 (hours 2 and 9).

At the month 3 or exit visit, a statistically significantly greater "yes" response to the Investigator

Pharmacoeconomic Evaluation was recorded for patients receiving Combination (91.1%, 173/190) than for patients receiving Brimonidine (73.4%, 141/192, p<0.001). A "yes" response was recorded for 92.7% (179/193) of patients receiving Timolol. There were no statistically significant differences in the change from baseline in treatment comfort between Combination and each of the monotherapy groups.

Treatment satisfaction was better than baseline for a statistically significantly greater percentage of patients in the Combination group (23.4%, 36/154) than in the Brimonidine group (13.2%, 20/151, p=0.005). A total of 19.9% (30/151) of patients in the Timolol group reported better treatment satisfaction than baseline.

Safety:

Through month 3 of the study, 53.4% (103/193) of patients in the Combination group, 61.7% (121/196) of the Brimonidine group, and 50.8% (100/197) of the Timolol group experienced one or more adverse events, regardless of causality. The incidences of oral dryness, eye pruritus, foreign body sensation and conjunctival folliculosis were statistically significantly lower with the Combination than with Brimonidine (p.ltoreq.0.034), while burning and stinging were statistically significantly higher with the Combination than with Brimonidine (p.ltoreq.0.028). There were no statistically significant differences in adverse events between the Combination and Timolol, except for a statistically significantly higher incidence of eye discharge with the Combination (2.6%, 5/193) compared to Timolol (0%, 0/197; p=0.029). The most frequently reported adverse events (>3% in any treatment group) were as follows, tabulated by descending order in the Combination group:

TABLE-US-00002 Combination Brimonidine Timolol Preferred Term N = 193 N = 196 N = 197 burning sensation in eye 23 (11.9%) 11 (5.6%) 25 (12.7%) conjunctival hyperemia 16 (8.3%) 23 (11.7%) 11 (5.6%) stinging sensation eye 13 (6.7%) 4 (2.0%) 11 (5.6%) infection (body as a 11 (5.7%) 6 (3.1%) 8 (4.1%) whole) visual disturbance 6 (3.1%) 11 (5.6%) 3 (1.5%) epiphora 5 (2.6%) 8 (4.1%) 3 (1.5%) oral dryness 4 (2.1%) 19 (9.7%) 1 (0.5%) eye pruritus 3 (1.6%) 13 (6.6%) 3 (1.5%) allergic conjunctivitis 3 (1.6%) 7 (3.6%) 0 (0.0%) asthenia 3 (1.6%) 6 (3.1%) 1 (0.5%) foreign body sensation 2 (1.0%) 10 (5.1%) 5 (2.5%) conjunctival folliculosis 2 (1.0%) 9 (4.6%) 1 (0.5%) somnolence 2 (1.0%) 7 (3.6%) 0 (0.0%)

Adverse events led to the discontinuation of 3.6% (7/193) of patients in the Combination group, similar to 3.0% (6/197) of patients in the Timolol group, and statistically significantly less than 14.3% (28/196) of patients in the Brimonidine group (p<0.001). Serious adverse events were reported for 1.0% (2/193) of patients in the Combination group, 2.0% (4/196) of patients in the Brimonidine group, and 2.0% (4/197) of patients in the Timolol group. Two patients receiving Timolol had 4 serious adverse events (emphysema in one patient; nausea, sweating, and tachycardia in the other patient) which were considered possibly related to the study drug. There was 1 death in the Brimonidine group, possibly due to complications from cardiac surgery, and not related to study drug.

There were no clinically relevant differences between the Combination and either of the individual components in the mean change from baseline to month 3 for any hematology, chemistry, or urinalysis parameter. Statistically significant (p.ltoreq.0.048) within-group changes from baseline were found, but were small and not clinically relevant.

Small but statistically significant (p.ltoreq.0.001) mean reductions in heart rate ranging from -2.1 to -3.7 bpm were seen with the Combination, similar to Timolol. Small but statistically significant (p.ltoreq.0.003) mean reductions in blood pressure at hour 2 (postdose) were seen with the Combination, similar to Brimonidine. These small changes in mean heart rate and blood pressure were associated with clinical symptoms in only a few patients.

Increases from baseline in the severity of conjunctival erythema and conjunctival follicles on biomicroscopy were statistically significantly less with the Combination than with Brimonidine (p.ltoreq.0.011). The majority of patients in each treatment group showed less than a 2-line change from baseline visual acuity. There were no significant between-group differences for changes in visual fields or cup/disc ratio.

Pharmacokinetics:

Blood samples were available for 55 patients in the Combination group, 49 patients in the Brimonidine group, and 54 patients in the Timolol group. All samples were assayed for both brimonidine (lower limit of quantitation [LLOQ] 5 pg/mL) and timolol (LLOQ 5 pg/mL). Plasma brimonidine and timolol concentrations were not quantifiable in all but 1 sample on day 0, hour 0 for both Combination and the monotherapy treatment groups.

In the Combination group, mean.+-.standard deviation (SD) plasma brimonidine concentrations 1 hour postdose at week 2 and month 3 were 49.7.+-.36.1 and 52.8.+-.46.7 pg/mL, respectively. In the Brimonidine group, mean.+-.SD plasma brimonidine concentrations at week 2 and month 3 were 81.0.+-.63.8 and 78.6.+-.48.9 pg/mL, respectively. In the Combination group, mean.+-.SD plasma timolol concentrations at week 2 and month 3 were 0.499.+-.0.327 and 0.586.+-.0.580 ng/mL, respectively. In the Timolol group, mean.+-.SD plasma timolol concentrations at week 2 and month 3 were 0.950.+-.0.709 and 0.873.+-.0.516 ng/mL, respectively.

Plasma brimonidine and timolol concentrations 1 hour postdose were steady and did not increase over the 3-month study duration. Brimonidine concentrations were 39%, 34% and 39% lower in the Combination group than in the monotherapy group at week 2 (p=0.004), month 3 (p=0.013), and month 12, respectively. Timolol concentrations were 47% and 33% lower in the Combination group than in the monotherapy group at week 2 (p<0.001) and month 3 (p=0.011), respectively.

Timolol concentrations were also significantly lower in the combination treatment group than in the Timolol monotherapy treatment group (p=0.0006). Timolol concentrations were 49%, 32%, and 21% lower in the combination group than in the monotherapy group at week 2, month 3, and month 12, respectively.

The plasma brimonidine concentration in males was statistically significantly lower than in females for the Brimonidine group (37% lower at week 2 [p=0.034] and 37% lower at month 3 [p=0.017]); the difference was not statistically significant in the Combination group. The plasma timolol concentration in males was statistically significantly lower than in females for both the Combination group (not statistically significant at week 2; 52% lower at month 3 [p=0.012]) and the Timolol group (45% lower at week 2 [p=0.006] and 39% lower at month 3 [p=0.003]).

Plasma brimonidine concentration in the elderly group was not significantly different from in the young group for the combined data from both the combination and Brimonidine treatment groups (p-value=0.1323). However, plasma timolol concentration in the young group was significantly lower than in the elderly group for combined data from both the combination and the Timolol treatment groups (p-value=0.0005).

Conclusions:

The Combination treatment (brimonidine tartrate 0.2%/timolol 0.5%) administered BID for 3 months was superior to Timolol (timolol 0.5%) BID and Brimonidine (brimonidine tartrate 0.2%) TID in

lowering the elevated IOP of patients with glaucoma or ocular hypertension. The Combination administered BID demonstrated a favorable safety profile that was comparable to Timolol BID and better than Brimonidine TID with regard to the incidence of adverse events and discontinuations due to adverse events.

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

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United States Patent **7,375,111**
Weber , et al. **May 20, 2008**

Compositions for affecting weight loss

Abstract

Disclosed are compositions for affecting weight loss comprising a first compound and a second compound, where the first compound is an opioid antagonist and the second compound causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiological conditions. Also disclosed are methods of affecting weight loss, increasing energy expenditure, increasing satiety in an individual, or suppressing the appetite of an individual, comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

Inventors: **Weber; Eckard** (San Diego, CA), **Cowley; Michael Alexander** (Portland, OR)
Assignee: **Orexigen Therapeutics, Inc.** (San Diego, CA)
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Primary Examiner: Kwon; Brian
Attorney, Agent or Firm: Knobbe, Martens, Olson and Bear LLP

Parent Case Text

RELATED APPLICATIONS

The present application claims priority to the Provisional Application Ser. No. 60/466,838, filed on Apr. 29, 2003, by Weber et al., and entitled "COMPOSITIONS FOR AFFECTING WEIGHT LOSS," the entire disclosure of which is incorporated herein by reference in its entirety.

Claims

What is claimed is:

1. A composition for affecting weight loss comprising: (a) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in an individual; and (b) a sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance the weight loss effect of the bupropion or salt thereof; wherein said composition is in a single oral dosage form fixed combination.

2. The composition of claim 1, wherein said composition comprises about 5 mg to about 50 mg of naltrexone or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1, wherein said composition comprises about 30 mg to about 500 mg of bupropion or a pharmaceutically acceptable salt thereof.

4. The composition of claim 1, wherein said composition comprises about 5 mg to about 50 mg of naltrexone or a pharmaceutically acceptable salt thereof, and about 30 mg to about 500 mg of bupropion or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition for affecting weight loss comprising: (a) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in an individual; (b) a sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance the weight-reducing effect of the bupropion or salt thereof; and a pharmaceutically acceptable excipient, diluent, or carrier, wherein said composition is formulated into a single oral fixed combination dosage form.

6. The pharmaceutical composition of claim 5, wherein said composition comprises about 5 mg to about 50 mg of naltrexone or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 5, wherein said composition comprises about 30 mg to about 500 mg of bupropion or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of claim 5, wherein said composition comprises about 5 mg to about 50 mg of naltrexone or a pharmaceutically acceptable salt thereof, and about 30 mg to about 500 mg of bupropion or a pharmaceutically acceptable salt thereof.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of pharmaceutical compositions and methods for the treatment of obesity and for affecting weight loss in individuals.

2. Description of the Related Art

Obesity is a disorder characterized by the accumulation of excess fat in the body. Obesity has been recognized as one of the leading causes of disease and is emerging as a global problem. Increased instances of complications such as hypertension, non-insulin dependent diabetes mellitus, arteriosclerosis, dyslipidemia, certain forms of cancer, sleep apnea, and osteoarthritis have been related to increased instances of obesity in the general population.

Obesity has been defined in terms of body mass index (BMI). BMI is calculated as weight (kg)/[height (m)].sup.2. According to the guidelines of the U.S. Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) (World Health Organization. Physical status: The use and interpretation of anthropometry. Geneva, Switzerland: World Health Organization 1995. WHO Technical Report Series), for adults over 20 years old, BMI falls into one of these categories: below 18.5 is considered underweight, 18.5-24.9 is considered normal, 25.0-29.9 is considered overweight, and 30.0 and above is considered obese.

Prior to 1994, obesity was generally considered a psychological problem. The discovery of the adipostatic hormone leptin in 1994 (Zhang et al., "Positional cloning of the mouse obese gene and its human homologue," Nature 1994; 372:425-432) brought forth the realization that, in certain cases, obesity may have a biochemical basis. A corollary to this realization was the idea that the treatment of obesity may be achieved by chemical approaches. Since then, a number of such chemical treatments have entered the market. The most famous of these attempts was the introduction of Fen-Phen, a combination of fenfluramine and phentermine. Unfortunately, it was discovered that fenfluramine caused heart-valve complications, which in some cases resulted in the death of the user. Fenfluramine has since been withdrawn from the market. There has been some limited success with other combination therapy approaches, particularly in the field of psychological eating disorders. One such example is Devlin, et al., Int. J. Eating Disord. 28:325-332, 2000, in which a combination of phentermine and fluoxetine showed some efficacy in the treatment of binge eating disorders. Of course, this disorder is an issue for only a small portion of the population.

In addition to those individuals who satisfy a strict definition of medical obesity, a significant portion of the adult population is overweight. These overweight individuals would also benefit from the availability of an effective weight-loss composition. Therefore, there is an unmet need in the art to

provide pharmaceutical compositions that can affect weight loss without having other adverse side effects.

SUMMARY OF THE INVENTION

Disclosed are compositions for affecting weight loss comprising a first compound and a second compound, where the first compound is an opioid antagonist and the second compound causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiological conditions.

Also disclosed are methods of affecting weight loss, increasing energy expenditure, increasing satiety in an individual, or suppressing the appetite of an individual, comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Arcuate nucleus neurons are known to be responsive to a wide array of hormones and nutrients, including leptin, insulin, gonadal steroids, and glucose. In addition to potential transport mechanisms, peripheral substances may access these neurons via arcuate cell bodies in and projections to the median eminence, a region considered to be a circumventricular organ, which lacks a blood-brain barrier. Cone et al., "The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis," Int'l Journal of Obesity (2001) 25, Suppl 5, S63-S67.

Administration of exogenous leptin activates a number of different neurons in hypothalamic and brainstem cell groups that bear leptin receptor. Leptin-responsive neurons in the arcuate nucleus include both those containing neuropeptide Y (NPY) and agouti-related peptide (AgRP) in the medial part of the nucleus and those containing both pro-opiomelanocortin (POMC) and its derivatives, including .alpha.-melanocyte stimulating hormone (.alpha.-MSH), as well as cocaine and amphetamine-related transcript (CART). Saper et al., "The need to feed: Homeostatic and hedonic control of eating," Neuron, 36:199-211 (2002).

The leptin-responsive POMC neurons in the arcuate nucleus are thought to cause anorexia and weigh reduction by means of the action of .alpha.-MSH on melanocortin 3 and/or 4 receptors (MC3-R, MC4-R). The highest MC3-R expression level is in the hypothalamus and limbic system, whereas MC4-R mRNA is expressed in virtually all major brain regions. Some of the metabolic effects resulting from stimulation of MC4-R are decreased food intake and an increase in energy expenditure through stimulation of thyrotropin-releasing hormone and activation of the sympathetic nervous system. Targeted deletion of the MC4-R gene produces obesity, hyperphagia, hyperinsulinemia, and reduced energy expenditure. Targeted deletion of MC3-R results in increased adiposity due to decreased energy expenditure. Korner et al., "The emerging science of body weight regulation and its impact on obesity treatment," J. Clin. Invest. 111(5):565-570 (2003). Thus, increased concentrations of .alpha.-MSH in the central nervous system (CNS) increase its action on MC3-R and/or MC4-R and result in a suppressed appetite.

POMC neurons also release .beta.-endorphin when they release .alpha.-MSH. .beta.-endorphin is an endogenous agonist of the 1-opioid receptors (MOP-R), found on the POMC neurons. Stimulation of MOP-R decreases the release of .alpha.-MSH. This is a biofeedback mechanism that under normal physiological conditions controls the concentration of .alpha.-MSH in the CNS. Thus, blocking MOP-R by opioid antagonists will break the feedback mechanism, which results in continued secretion of .alpha.-MSH and an increase in its concentration in the CNS.

A second population of neurons in the arcuate nucleus tonically inhibits the POMC neurons. These POMC-inhibiting neurons secrete NPY, the neurotransmitter .gamma.-aminobutyric acid (GABA), and AgRP. NPY and GABA inhibit POMC neurons, via NPY Y1 receptors and GABA receptors, respectivley. Thus, within the arcuate nucleus NPY and GABA inhibit the release of .alpha.-MSH, and therefore are stimulators of feeding. It is known that leptin inhibits the release of GABA from NPY terminals synapsing onto POMC neurons, whereas ghrelin, an orexigenic peptide, stimulates the ghrelin receptors on NPY neurons and increase the secretion of NPY and GABA onto the POMC cells, which in turn inhibits the release of .alpha.-MSH.

AgRP stimulates food intake in the rat through antagonism of the interaction of .alpha.-MSH at MC4-R. Expression of the AgRP gene is suppressed by leptin.

Serotonin, also known as 5-hydroxytryptamine or 5-HT, activates the POMC neurons to secrete .alpha.-MSH. However, serotonin is taken up and removed from action by specific transporters so that a single serotonin molecule has short term effects. It is known that selective serotonin re-uptake inhibitors (SSRIs) prevent the uptake of serotonin and increase its concentrations in the CNS. Thus, SSRIs also increase the secretion of .alpha.-MSH and its concentrations in the CNS.

Therefore, increased secretion of .alpha.-MSH through various mechanisms, such as serotonin re-uptake inhibition, are among the strategies that the methods and pharmaceutical compositions of the present invention pursue in order to produce a biochemical anorexigenic effect.

The present invention provides a multi-faceted combination therapy approach to the problem of weight loss. It addresses not just single molecules, messengers, or receptors, but instead acts on multiple points in the feeding and satiety pathway. Aspects of the present invention are directed to increasing the concentrations of .alpha.-MSH in the CNS by stimulating the release of A-MSH, suppressing its metabolism, reducing the antagonism of its interaction at MC3/4-R, and suppressing any feedback mechanisms that slow or stop its release. Aspects of the present invention include pharmaceutical compositions whose components achieve one or more of these functions. The present inventors have discovered that a combination of two or more of the compounds disclosed herein results in a synergistic effect that affects weight loss more quickly and on a more permanent basis.

Thus, in a first aspect, the present invention is directed to a composition for the treatment of obesity or for affecting weight loss comprising a first compound and a second compound, where the first compound is an opioid antagonist and the second compound causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiological conditions.

In certain embodiments, the second compound causes increased activity of the POMC neurons, leading to greater agonism at MC3-R and/or MC4-R.

In certain embodiments the opioid antagonist antagonizes a .mu.-opioid receptor (MOP-R) in a mammal. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans.

In some embodiments the opioid antagonist is selected from the group consisting of alvimopan, norbinaltorphimine, nalmefene, naloxone, naltrexone, methylnaltrexone, and nalorphine, and pharmaceutically acceptable salts or prodrugs thereof.

In other embodiments, the opioid antagonist is a partial opioid agonist. Compounds of this class have

some agonist activity at opioid receptors. However, because they are weak agonists, they function as de-facto antagonists. Examples of partial opioid agonists include pentacozine, buprenorphine, nalorphine, propiram, and lofexidine.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl) methylamine, and salts thereof with amino acids such as arginine, lysine, and the like.

A "prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug, or may demonstrate increased palatability or be easier to formulate. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to provide the active moiety.

In certain embodiments, the second compound in the pharmaceutical compositions of the present invention triggers the release of .alpha.-melanocyte stimulating hormone (.alpha.-MSH). The second compound may increase the extracellular serotonin concentrations in the hypothalamus. In some embodiments, the second compound is selected from the group consisting of a selective serotonin reuptake inhibitor (SSRI), a serotonin 2C agonist, and a serotonin 1B agonist. In further embodiments, the second compound is selected, e.g., from the group consisting of fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, sibutramine, duloxetine, atomoxatine, and venlafaxine, and pharmaceutically acceptable salts or prodrugs thereof.

The terms "serotonin 1B receptor," "serotonin 2C receptor," "5-HT1b receptor," and "5-HT2c receptor" refer to receptors found more commonly in rodents. It is understood by those of skill in the art that other mammals have serotonin receptors on various neurons that are analogous in function and form to these receptors. Agonists or antagonists at these non-rodent, preferably human, serotonin receptors are within the scope of the present invention.

In certain embodiments, the second compound suppresses the expression of the AgRP gene or the production or release of agouti-related protein (AgRP). In some of these embodiments, the second compound suppresses the activity of neurons that express AgRP.

In other embodiments, the second compound suppresses the expression of the NPY gene or the production or release of neuropeptide Y (NPY). In some of these embodiments, the second compound suppresses the activity of neurons that express NPY. In further embodiments, the second compound is selected from the group consisting of NPY antagonists, ghrelin antagonists, and leptin. In certain other embodiments, the second compound agonizes NPY Y2 receptor.

Other embodiments of the present invention include those in which the second compound is selected from the group consisting of a .gamma.-amino butyric acid (GABA) inhibitor, a GABA receptor antagonist, and a GABA channel antagonist. By "GABA inhibitor" it is meant a compound that reduces the production of GABA in the cells, reduces the release of GABA from the cells, or reduces the activity of GABA on its receptors, either by preventing the binding of GABA to GABA receptors or by minimizing the effect of such binding. The GABA inhibitor may be a 5-HT1b agonist or another agent that inhibits the activity of NPY/AgRP/GABA neurons. In addition, the GABA inhibitor may suppress the expression of the AgRP gene, or the GABA inhibitor may suppress the production or release of AgRP. It is, however, understood that a 5-HT1b agonist may inhibit the NPY/AgRP/GABA neuron (and therefore activate POMC neurons) without acting as an inhibitor of the GABA pathway.

In certain other embodiments the GABA inhibitor increases the expression of the POMC gene. In some of these embodiments, the GABA inhibitor increases the production or release of pro-opiomelanocortin (POMC) protein. In certain other of these embodiments, the GABA inhibitor increases the activity on POMC expressing neurons. In some embodiments, the GABA inhibitor is topiramate.

In other embodiments the second compound is a dopamine reuptake inhibitor. Phentermine is an example of a dopamine reuptake inhibitor. In certain other embodiments, the second compound is a norepinephrine reuptake inhibitor. Examples of norepinephrine reuptake inhibitors include bupropion, thionisoxetine, and reboxetine. Other embodiments include those in which the second compound is a dopamine agonist. Some dopamine agonists that are available on the market include cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine. In further embodiments, the second compound is a norepinephrine releaser, for example diethylpropion, or a mixed dopamine/norepinephrine reuptake inhibitor, for example, atomoxatine.

In certain other embodiments, the second compound is a 5-HT1b agonist, such as sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, and elitriptan.

In further embodiments, the second compound is an anticonvulsant. The anticonvulsant may be selected from the group consisting of zonisamide, topiramate, nembutal, lorazepam, clonazepam, clorazepate, tiagabine, gabapentin, fosphenyloin, phenyloin, carbamazepine, valproate, felbamate, levetiracetam, oxcarbazepine, lamotrigine, methsuximide, and ethosuxmide.

In some embodiments, the second compound is a cannabinoid receptor antagonist. Examples of this group of compounds include AM251 [N-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-p- yrazole-3-carboxamide], AM281 [N-(morpholin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-p- yrazole-3-carboxamide], AM630 (6-iodo-2-methyl-1-[2-(4-morpholinyl) ethyl]-1H-indol-3-yl](4-methoxypheny- l)methanone), LY320135, and SR141716A (rimonabant), and pharmaceutically acceptable salts or prodrugs thereof. LY320135 and SR141716A have the following structures.

##STR00001##

In certain embodiments, the second compound itself may be a combination of two or more compounds. For example, the second compound may be a combination of a dopamine reuptake inhibitor and a norepinephrine reuptake inhibitor, e.g. bupropion and mazindol. Alternatively, the second compound may be a combination of a SSRI and a norepinephrine reuptake inhibitor, such as sibutramine, venlafaxine, and duloxetine.

In certain embodiments, the second compound is an activator of the POMC neurons. Examples of POMC activators include Ptx1 and interleukin 1 beta, (IL-1.beta.).

In another aspect, the present invention relates to a method of affecting weight loss, comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In certain embodiments, the individual has a body mass index (BMI) greater than 25. In other embodiments, the individual has a BMI greater than 30. In still other embodiments, the individual has a BMI greater than 40. However, in some embodiments, the individual may have a BMI less than 25. In these embodiments, it may be beneficial for health or cosmetic purposes to affect weight loss, thereby reducing the BMI even further.

In some embodiments, opioid receptor activity is antagonized by administering an opioid receptor antagonist. The opioid receptor antagonist may be a MOP receptor antagonist. In some embodiments, the opioid receptor antagonist is selected from alvimopan, norbinaltorphimine, nalmefene, naloxone, naltrexone, methylnaltrexone, and nalorphine, and pharmaceutically acceptable salts or prodrugs thereof.

In some of the embodiments set forth above, .alpha.-MSH activity is enhanced by administering a compound, where the compound triggers release of .alpha.-MSH or increases the activity of neurons that express .alpha.-MSH. In some embodiments, the compound is a selective serotonin reuptake inhibitor (SSRI) or a specific 5-HT receptor agonist. Examples of SSRIs that can be used in the present invention include fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, sibutramine, duloxetine, and venlafaxine, and pharmaceutically acceptable salts or prodrugs thereof.

In other embodiments, the compound is a .gamma.-amino butyric acid (GABA) inhibitor. The GABA inhibitor may be a 5-HT1b receptor agonist. The GABA inhibitor may suppress the expression of the AgRP gene, or it may suppresses the production or release of AgRP. The GABA inhibitor may suppress the expression or release of NPY. In certain embodiments, the GABA inhibitor suppresses the activity of neurons that express AgRP. For example, the GABA inhibitor may be topiramate, 1-(2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinec- arboxylic acid hydrochloride (NNC-711), or vigabatrin.

In certain embodiments, the method of invention set forth above is practiced with the proviso that the individual is not suffering from Prader-Willi syndrome or binge eating disorder. Thus, some embodiments of the invention are to be distinguished from combination therapy involving SSRI anti-depressants (e.g., fluoxetine) used to treat physiological eating disorders such as binge eating disorder or Prader-Willi syndrome. In these embodiments, the target population is the population of individuals needing or desiring weight loss, apart from needing treatment for Prader-Willi syndrome or binge eating disorder.

Individuals suffering from depression may gain weight as a result of their depression. In addition, certain depressed individuals gain weight as a side effect of the depression therapy. In certain embodiments, the method of invention set forth above is practiced with the proviso that the individual is not suffering from depression. In some embodiments, the individual's overweight state was not caused by treatment for depression.

In other embodiments, the method of the invention set forth above is practiced with the proviso that if the opioid receptor is antagonized using naltrexone, then release of .alpha.-MSH is not stimulated with fluoxetine. However, the combination of naltrexone with fluoxetine may be used to affect weight loss in individuals who wish to lose weight, whether or not they are clinically categorized as obese. These individuals may include those with BMI of greater than 25, or those individuals with BMI of less than

25 who still wish to lose additional weight. This particular combination may also be used for the treatment of general obesity. In certain embodiments, the individual who wishes to lose additional weight does not suffer from binge eating disorder.

In some embodiments, the treating step of the above method comprises administering to the individual a first compound and a second compound, where the first compound is an opioid antagonist and the second compound enhances .alpha.-MSH activity.

In some embodiments the first compound and the second compound are administered more or less simultaneously. In other embodiments the first compound is administered prior to the second compound. In yet other embodiments, the first compound is administered subsequent to the second compound.

In certain embodiments, the first compound and the second compound are administered individually. In other embodiments, the first compound and the second compound are covalently linked to each other such that they form a single chemical entity. The single chemical entity is then digested and is metabolized into two separate physiologically active chemical entities, one of which is the first compound and the other one is the second compound.

In some embodiments, the compositions of the present invention are a combination of the following compounds: a SSRI in combination with a dopamine reuptake inhibitor, a dopamine/norepinephrine reuptake inhibitor, a norepinephrine reuptake inhibitor, an opioid antagonist, a partial opioid agonist, GABA inhibitor, a peripherally acting weight loss agent such as metformin, or a peptide, such as PYY, PYY.sub.3-36, or leptin; Serotonin in combination with a dopamine reuptake inhibitor, a dopamine/norepinephrine reuptake inhibitor, an opioid antagonist, a partial opioid agonist, or a GABA inhibitor; a dopamine reuptake inhibitor in combination with a norepinephrine reuptake inhibitor, a norepinephrine releaser, a norepinephrine agonist, an opioid antagonist, a partial opioid agonist, a GABA inhibitor, an adenosine compound, a cholinergic receptor antagonist, or a peptide, such as PYY, PYY.sub.3-36, or leptin; a dopamine/norepinephrine reuptake inhibitor in combination with an opioid antagonist, a partial opioid agonist, a GABA inhibitor, or a peripherally acting weight loss agent such as metformin; a dopamine agonist in combination with an opioid antagonist, a partial opioid agonist, a GABA inhibitor, or a peptide, such as PYY, PYY.sub.3-36, or leptin.

Examples of norepinephrine agonists include phendimetrazine and benzphetamine. Examples of adenosine compounds include all xanthine derivatives, such as adenosine, caffeine, theophylline, theobromine, and aminophylline. An example of acholinergic receptor antagonist is nicotine.

In another aspect, the present invention relates to a method of increasing satiety in an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In some embodiments, the treating step of the above method comprises administering to the individual a first compound and a second compound, where the first compound is an opioid antagonist and the second compound enhances .alpha.-MSH activity.

In some embodiments the first compound and the second compound are administered nearly simultaneously. In other embodiments the first compound is administered prior to the second compound. In yet other embodiments, the first compound is administered subsequent to the second compound.

In yet another aspect, the present invention relates to a method of suppressing the appetite of an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In some embodiments, the treating step of the above method comprises administering to the individual a first compound and a second compound, where the first compound is an opioid antagonist and the second compound enhances .alpha.-MSH activity.

In some embodiments the first compound and the second compound are administered nearly simultaneously. In other embodiments the first compound is administered prior to the second compound. In yet other embodiments, the first compound is administered subsequent to the second compound.

In another aspect, the present invention relates to a method of increasing energy expenditure in an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In some embodiments, the treating step of the above method comprises administering to the individual a first compound and a second compound, where the first compound is an opioid antagonist and the second compound enhances .alpha.-MSH activity.

In some embodiments the first compound and the second compound are administered nearly simultaneously. In other embodiments the first compound is administered prior to the second compound. In yet other embodiments, the first compound is administered subsequent to the second compound.

In certain embodiments disclosed herein, an individual is given a pharmaceutical composition comprising a combination of two or more compounds to affect weight loss. In some of these embodiments, each compound is a separate chemical entity. However, in other embodiments, the two compounds are joined together by a chemical linkage, such as a covalent bond, so that the two different compounds form separate parts of the same molecule. The chemical linkage is selected such that after entry into the body, the linkage is broken, such as by enzymatic action, acid hydrolysis, base hydrolysis, or the like, and the two separate compounds are then formed.

Thus, in another aspect, the present invention relates to synthetic routes to novel molecules in which an opioid antagonist is linked by a flexible linker to a selective serotonin reuptake inhibitor (SSRI).

Data from previous structure-activity relationship (SAR) studies within the family of .mu. opioid antagonists may be used as a guide to determine which antagonists to use and the optimal position or positions on the antagonist molecules to attach the tether such that potency and selectivity of the antagonist will remain high. Similarly, SAR data within the family of SSRIs may be used as a guide to determine which inhibitors to use and the optimal position or positions on the inhibitors to attach the tether such that potency and selectivity remain high. The tether or linker moiety is chosen from among those of demonstrated utility for linking bioactive molecules together. Disclosed herein are representative opioid antagonists, linkers and SSRI molecules that can be attached together in different combinations to form heterobivalent therapeutic molecules.

Structure-activity relationships of the opioid agonists and antagonists have been reviewed. See for example, Zimmerman, D. M.; Leander, J. D. J. Med. Chem. 1990, 33, 895; Portoghese, P. S. J. Med. Chem. 1992, 35, 1927; Carroll, F. I. J. Med. Chem. 2003, 46, 1. The opioid antagonists, nalmefene (1), naltrexone (2), naloxone (3) and naltrexamine (4) are thebaine-derived structures that share a common opiate-type template. 1-Subtype selective opioid antagonists are of considerable current interest as agents for the treatment of obesity (Glass, M. J.; Billington, C. J.; Levine, A. S. Neuropeptides 1999, 33, 350) and CNS disorders (Reneric, J. P.; Bouvard, M. P. CNS Drugs 1998, 10, 365).

##STR00002##

N-Methyl and N-2-phenylethyl substituted opioids tend to show opioid agonist activity whereas N-allyl and N-cyclopropylmethyl substituted analogs tend to show opioid antagonist activity. Any N-attached linker moiety will be larger than methyl. Provided that the linker moiety does not mimic 2-phenylethyl, such linked opioids are expected to behave as opioid antagonists. Therefore, the nitrogen atom of nalmefene and naltrexone (and naloxone) is a suitable site for attachment of a linker moiety. Less SAR information is available with regard to substitution at other sites on these opioids, however, attachment of the linker unit to one or the other of the carbon atoms bearing one or more hydrogen atoms remains an option.

Both nalmefene and naltrexone are potent .mu.-opioid antagonists. The only structural difference is that nalmefene has a methylene group in place of the ketone oxygen atom in naltrexone. It is thus postulated that significant changes in structure at the ketone oxygen site in naltrexone do not significantly affect antagonist potency. Therefore, a linker may be attached to the methylene group in nalmefene without significant reduction in antagonist potency. Carbonyl derivatives of naloxone are well known and include symmetrical azine (.dbd.N--N.dbd.), mixed azine (Schmidhammer, H.; Kaspar, F.; Marki, A.; Borsodi, A. Helv. Chim. Acta 1994, 77, 999), hydazone (Hahn, E. F.; Itzhak, Y.; Nishimura, S.; Johnson, N.; Pasternak, G. W. J. Pharm. Exper. Therapeutics 1985, 235, 846-50), semicarbazone and thiosemicarbazone derivatives (Kolb, V. M.; Koman, A.; Neil, A. Pharmaceutical Res. 1985, 6, 266-71). Naloxazone, the hydrazone of naloxone, is an irreversible, selective and long acting antagonist of the .mu.-1 subclass of the opioid receptors (Pasternak, G. W.; Hahn, E. F. J. of Med. Chem. 1980, 23, 674-6). Certain of the derivatives are potent .mu. opioid antagonists while others are potent agonists.

Naltrexamine (4) has been linked by attachment of its primary amino group to a wide variety of other molecules producing, for example, a fluorogenic opioid receptor affinity label (Le Bourdonnec, B.; El Kouhen, R.; Lunzer, M. M.; Law, P. Y.; Loh, H. H.; Portoghese, P. S.; J. Med. Chem.; 2000; 43; 2489-2492), an extensive series of nonequilibrium opioid agonists and antagonists (Sayre, L. M.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. J. Med. Chem. 1984, 27, 1325), and a series of potent bivalent opioid antagonists (Erez, M.; Takemori, A. E.; Portoghese, P. S. J. Med. Chem. 1982, 25, 847-849). Consequently, the primary amino group of naltrexamine constitutes a suitable site for attachment of a linker moiety.

##STR00003##

A limited SAR for fluoxetine (5) has been published in U.S. Pat. No. 4,214,081, incorporated by reference herein in its entirety. N-Methylfluoxetine (6) shows comparable potency and selectivity to that of fluoxetine toward inhibition of serotonin reuptake. Therefore, attachment of a linker to the nitrogen atom of fluoxetine can result in retention of the potency and selectivity of fluoxetine itself. However, the present disclosure is not limited to the fluoxetine series of SSRIs. It is envisaged that a variety of SSRI molecules such as paroxetine (Dechant, K. L.; Clissold, S. P. Drugs, 1991, 41, 225-253) or one or the other of the bivalent SSRIs described by Kozikowski et al. (Tamiz, A. P.; Zhang, J.; Zhang, M.; Wang, C. Z.; Johnson, K. M.; Kozikowski, A. P. J. Am. Chem. Soc. 2000, 122, 5393-5394; Tamiz, A. P.; Bandyopadhyay, B. C.; Zhang, J.; Flippen-Anderson, J. L.; Zhang, M.; Wang, C. Z.; Johnson, K. M.; Tella, S.; Kozikowski, A. P. J. Med. Chem. 2001, 44, 1615-1622) may also be utilized to construct the heterobivalent therapeutic molecules of this invention.

Examples of linkers reported in the scientific literature include methylene (CH.sub.2).sub.n linkers (Hussey, S. L.; Muddana, S. S.; Peterson, B. R.; J. Am. Chem. Soc. 2003; 125; 3692-3693; Tamiz, A. P.; Bandyopadhyay, B. C.; Zhang, J.; Flippen-Anderson, J. L.; Zhang, M.; Wang, C. Z; Johnson, K. M.; Tellar, S.; Kozikowski, A. P. J. Med. Chem. 2001, 44, 1615-1622), oligo ethyleneoxy O(--CH.sub.2CH.sub.2O--).sub.n units used to link naltrexamine to other opioids, glycine oligomers of the

formula --NH--(COCH.sub.2NH).sub.nCOCH.sub.2CH.sub.2CO--(NHCH.sub.2CO).sub.nNH-- used to link opioid antagonists and agonists together ((a) Portoghese, P. S.; Ronsisvalle, G.; Larson, D. L.; Yim, C. B.; Sayre, L. M.; Takemori, A. E. Life Sci. 1982, 31, 1283-1286. (b) Portoghese, P. S.; Larson, D. L.; Sayre, L. M.; Yim, C. B.; Ronsisvalle, G.; Tam, S. W.; Takemori, A. E. J. Med. Chem. 1986, 29, 1855-1861), hydrophilic diamines used to link opioid peptides together (Stepinski, J.; Zajaczkowski, I.; Kazem-Bek, D.; Temeriusz, A.; Lipkowski, A. W.; Tam, S. W. Internat. J. of Peptide & Protein Res. 1991, 38, 588-92), rigid double stranded DNA spacers (Paar, J. M.; Harris, N. T.; Holowka, D.; Baird, B. J. Immunol. 2002, 169, 856-864) and the biodegradable linker poly (L-lactic acid) (Klok, H.-A.; Hwang, J. J.; Iyer, S. N.; Stupp, S. I. Macromolecules 2002, 35, 746-759). The attachment of the tether to the antagonist can result in the antagonist achieving a favorable binding orientation. The linker itself may or may not be biodegradable. The linker may take the form of a prodrug and be tunable for optimal release kinetics of the linked drugs. The linker may be either conformationally flexible throughout its entire length or else a segment of the tether may be designed to be conformationally restricted (Portoghese, P. S.; Ronsisvalle, G.; Larson, D. L.; Takemori, A. E. J. Med. Chem. 1986, 29, 1650-1653).

In Scheme 1 below, naltrexone (2) is used in the linking reaction. As a consequence of the Wittig reaction, a double bond replaces the carbonyl group in naltrexone. The net result is fluoxetine linked with a flexible methylene linker to a nalmefene molecule by way of the nalmefene double bond.

##STR00004##

Reductive amination of fluoxetine with an .omega.-bromoaldehyde such as 11-bromoundecanal 6 (n=9) gives bromoamine 7 (n=9), best stored as the hydrobromide salt to prevent an unwanted slow macrocyclization side reaction by way of attack of the free amino group on the carbon bearing the bromine atom. Reaction of 7 with triphenylphosphine gives the intermediate phosphonium salt, which upon rection with butyllithium generates the corresponding ylid 8 (n=9). A Wittig reaction between 8 and the ketone group of naltrexone (2) gives the linked molecule 9 containing a fluoxetine unit coupled to what is now a nalmefene unit. The expected mixture of cis, trans isomers about the newly introduced double bond is separable by standard chromatographic techniques. If racemic fluoxetine is used, then a mixture of two optically active diastereomers of 9 will be produced owing to the fact that a single enantiomer 2 of naltrexone was used. Chemists skilled in the art will recognize that the (CH.sub.2).sub.9 linker may be varied in length and/or contain substituents by beginning with a different bromoaldehyde. Thus, pharmacological properties may be optimized. Molecule 9 is stable under physiological conditions. Opioid antagonist activity will be due to the covalently linked nalmefene unit and not due to free nalmefene released as a result of some cleavage reaction. Similarly, SSRI activity will be due to the covalently linked fluoxetine unit and not due to free fluoxetine released as a result of some cleavage reaction.

An analogous reaction sequence may be used in which the bromoaldehyde is derived from an oligo ethylene glycol as shown in Scheme 2 below. For example, tetraethylene glycol (10 n=2) is converted into bromide 11 (n=2), which is then oxidized under Swern conditions to aldehyde 12 (n=2). Substitution of aldehyde 12 for aldehyde 6 in Scheme 1 will give a series of irreversibly linked molecules in which the linker is more hydrophilic than that in molecules 9. Generation of the ylid in the oligo ethylene glycol series and the subsequent Wittig reaction is performed at reduced temperature to avoid .beta.-elimination of the alkoxy group. If racemic fluoxetine is used, then a mixture of two optically active diastereomers of 13 will be produced owing to the fact that a single enantiomer 2 of naltrexone was used. Chemists skilled in the art will recognize that the (OCH.sub.2CH.sub.2).sub.n linker may be varied in length by beginning with a different bromoaldehyde 12. Thus, pharmacological properties may be optimized. Molecule 13 is stable under physiological conditions.

##STR00005##

In Scheme 3, another linking method beginning with tetraethylene glycol is illustrated as an example of a variety of oligo ethylene glycols that may be used. Adapting the chemistry of Sashiwa et al. (Sashiwa, H.; Shigemasa, Y.; Roy, R. Macromolecules 2000, 33, 6913), tetraethylene glycol may be converted into acetal 14 (n=2) and subsequently into aldehyde 15. Reductive amination of fluoxetine with aldehyde 15 gives the fluoxetine derivative 16. Reduction of azide 16 to amine 17 and then reductive amination with naltrexone gives molecule 18 in which a fluoxetine unit is linked irreversibly by a flexible oligo ethyleneoxy unit to .beta.-naltrexamine (after separation of the .alpha. and .beta. isomers). If racemic fluoxetine is used, then a mixture of two optically active diastereomers of 18 will be produced owing to the fact that a single enantiomer 2 of naltrexone was used. Chemists skilled in the art will recognize that the (OCH.sub.2CH.sub.2).sub.n linker may be varied in length by beginning with a different oligo ethylene glycol 10. Thus, pharmacological properties may be optimized. Molecule 18 should be stable under physiological conditions.

##STR00006##

Scheme 4 illustrates a synthetic route to fluoxetine linked to nalmefene by way of the N-cyclopropyl group of nalmefene. The readily available t-butyldimethylsilyl protected noroxymorphone (19) is synthesized from morphine (Ninan, A.; Sainsbury, M. Tetrahedron 1992, 48, 6709-16), and then subjected to a reductive amination reaction with the commercially available cyclopropanecarboxaldehyde 20 (Aldrich, largely trans) giving ester 21. Wittig methyleneation gives ester 22, which is hydrolyzed to give acid 23. Activation of acid 23 with an appropriate carbodiimide and then N-acylation of fluoxetine derivative 17 (Scheme 3) gives 25, deprotection of which with Bu.sub.4NF gives the novel molecule 26. Chemists skilled in the art will recognize that the (OCH.sub.2CH.sub.2).sub.n linker may be varied in length by beginning with a different aldehyde azide 15 in the synthesis of 17. Thus, pharmacological properties may be optimized. Molecule 26 should be stable under physiological conditions.

Alternatively, ester 22 may be reduced to aldehyde 24 using DIBAL at -78.degree. C. Reductive amination of aldehyde 24 with amine 17 gives molecule 27 after removal of the TBDMS protecting group. Chemists skilled in the art will recognize that the (OCH.sub.2CH.sub.2).sub.n linker may be varied in length by beginning with a different aldehyde azide 15 in the synthesis of 17. Thus, pharmacological properties may be optimized. Molecule 27 should be stable under physiological conditions.

##STR00007##

If the Wittig methyleneation step is omitted in the above sequence, then an analog of 26, namely ketone 28, is formed in which the methylene group of 26 is replaced by a carbonyl group. The result is a naltrexone unit linked to a fluoxetine unit by way of a flexible, hydrophilic (CH.sub.2CH.sub.2O).sub.n linker in the form of compound 28. Chemists skilled in the art will recognize that the (OCH.sub.2CH.sub.2).sub.n linker may be varied in length by beginning with a different aldehyde azide 15 in the synthesis of 17. Thus, pharmacological properties may be optimized. Molecule 28 is stable under physiological conditions.

Scheme 5 illustrates how fluoxetine may be linked to .beta.-naltrexamine using a combination of linkers, namely the flexible glycine-based linkers 29 exploited by Portoghese et al. and the oligo ethylene glycol linkers used in the schemes above. Thus carboxyl activation of 29 with a suitable carbodiimide followed by monocondensation with .beta.-naltrexamine gives amide 30. Reactivation of 30 followed by condensation with amine 17 (Scheme 3) gives molecule 31. Portoghese reports that symmetrical amides

derived from linker 29 and .beta.-naltrexamine are effective .mu.-opioid receptor antagonists. Chemists skilled in the art will recognize that the --NH--(COCH.sub.2NH).sub.n-1COCH.sub.2CH.sub.2CO--(NHCH.sub.2CO).sub.nNH-- - linker may be varied in length by beginning with a different glycine-based linking unit 29 in the synthesis of 30. Thus, pharmacological properties may be optimized. Molecule 31 is stable under physiological conditions.

##STR00008##

Reaction of bromide 7 (Scheme 1) with Mg in dry THF will give Grignard reagent 32, reaction of which with the carbonyl group of naltrexone gives adduct 33 after separation of the two diastereomers produced at the newly created chiral center. Adduct 33 contains a fluoxetine segment linked to a N-cyclopropylmethyl-normorphine unit by way of a flexible methylene linker. Chemists skilled in the art will recognize that the (CH.sub.2).sub.9 linker may be varied in length by beginning with a different bromoaldehyde for the synthesis of bromide 7. Thus, pharmacological properties may be optimized. Molecule 33 is stable under physiological conditions.

##STR00009##

Throughout the above schemes, one should be able to employ N-desmethylfluoxetine (34), or any other derivative of fluoxetine, in place of fluoxetine. The resulting linked fluoxetine unit is identical to that of fluoxetine itself except that the methyl group of fluoxetine is replaced by a longer chain that is part of the linker. When necessary due to the use of strongly basic reagents or when chemoselectivity toward a primary amino group elsewhere in the molecule is required, one may protect the intermediate fluoxetine secondary amino group by use of the N-[2-(trimethylsilyl)ethoxy]methyl (SEM) group (Zeng, Z.; Zimmerman, S. C. Tetrahedron Lett. 1988, 29, 5123) as illustrated in Scheme 7.

##STR00010##

In another aspect, the invention relates to a pharmaceutical composition comprising a combination of an opioid antagonist and a compound that causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiological conditions, as described above, or comprising a linked molecule, as described herein, and a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The pharmaceutical compositions described herein can be administered to a human patient per se, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 18th edition, 1990.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; e.g., in Remington's Pharmaceutical Sciences, above.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be

used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80.TM., and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80.TM.; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Many of the compounds used in the pharmaceutical combinations of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl et al. 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. Note that for almost all of the specific compounds mentioned in the present disclosure, human dosages for treatment of at least some condition have been established. Thus, in most instances, the present invention will use those same dosages, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED.sub.50 or ID.sub.50 values, or other appropriate values derived from in vitro or in vivo studies, as qualified by toxicity studies and efficacy studies in animals.

Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient

may be, for example, an oral dose of between 0.1 mg and 500 mg of each ingredient, preferably between 1 mg and 250 mg, e.g. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of each ingredient between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg of each ingredient of the pharmaceutical compositions of the present invention or a pharmaceutically acceptable salt thereof calculated as the free base, the composition being administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of each ingredient up to 400 mg per day. Thus, the total daily dosage by oral administration of each ingredient will typically be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will typically be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present invention. Therefore, it should be clearly understood that the forms of the present invention are illustrative only and are not intended to limit the scope of the present invention.

Some Embodiments of the Invention

Some of the embodiments of the present invention are as follows:

In the first embodiment, the invention relates to a composition for affecting weight loss comprising a first compound and a second compound, wherein said first compound is an opioid antagonist and said

second compound causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiological conditions.

In the second embodiment, the invention relates to the composition of the first embodiment, wherein said opioid antagonist antagonizes an opioid receptor in a mammal.

In the third embodiment, the invention relates to the composition of the second embodiment, wherein said opioid receptor is selected from a .mu.-opioid receptor (MOP-R), a .eta.-opioid receptor, and a .delta.-opioid receptor.

In the fourth embodiment, the invention relates to the composition of the second embodiment, wherein said opioid antagonist antagonizes a .mu.-opioid receptor (MOP-R) in a mammal.

In the fifth embodiment, the invention relates to the composition of the first embodiment, wherein said opioid antagonist is selected from the group consisting of alvimopan, norbinaltorphimine, nalmefene, naloxone, naltrexone, methylnaltrexone, and nalorphine, and pharmaceutically acceptable salts or prodrugs thereof.

In the sixth embodiment, the invention relates to the composition of the first embodiment, wherein said opioid antagonist is a partial opioid agonist.

In the seventh embodiment, the invention relates to the composition of the sixth embodiment, wherein said partial opioid agonist is selected from the group consisting of pentacozine, buprenorphine, nalorphine, propiram, and lofexidine.

In the eighth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound triggers the release of .alpha.-melanocyte stimulating hormone (.alpha.-MSH).

In the ninth embodiment, the invention relates to the composition of the eighth embodiment, wherein said second compound increases the extracellular serotonin concentrations in the hypothalamus.

In the tenth embodiment, the invention relates to the composition of the ninth embodiment, wherein said second compound is selected from the group consisting of a selective serotonin reuptake inhibitor (SSRI), a serotonin 2C agonist, and a serotonin 1B agonist.

In the eleventh embodiment, the invention relates to the composition of the tenth embodiment, wherein said second compound is selected from the group consisting of fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, sibutramine, duloxetine, and venlafaxine, and pharmaceutically acceptable salts or prodrugs thereof.

In the twelfth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound suppresses the expression of the AgRP gene or the production or release of agouti-related protein (AgRP).

In the thirteenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound suppresses the activity of neurons that express AgRP.

In the fourteenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound suppresses the expression of the NPY gene or the production or release of neuropeptide Y (NPY).

In the fifteenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound suppresses the activity of neurons that express NPY.

In the sixteenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is selected from the group consisting of NPY Y1 receptor antagonists, ghrelin antagonists, and leptin.

In the seventeenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound agonizes NPY Y2 receptor.

In the eighteenth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is selected from the group consisting of a .gamma.-amino butyric acid (GABA) inhibitor, a GABA receptor antagonist, and a GABA channel antagonist.

In the nineteenth embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor is a 5-HT1b agonist, which may be selected from sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, and elitriptan.

In the twentieth embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor suppresses the expression of the AgRP gene.

In the twenty first embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor suppresses the production or release of AgRP.

In the twenty second embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor increases the expression of the POMC gene.

In the twenty third embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor increases the production or release of .alpha.-MSH from pro-opiomelanocortin (POMC) neurons.

In the twenty fourth embodiment, the invention relates to the composition of the eighteenth embodiment, wherein said GABA inhibitor increases the activity of POMC expressing neurons.

In the twenty fifth embodiment, the invention relates to the composition of the eighteenth embodiment, wherein the GABA inhibitor is topiramate.

In the twenty sixth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is a dopamine reuptake inhibitor.

In the twenty seventh embodiment, the invention relates to the composition of the twenty sixth embodiment, wherein said dopamine reuptake inhibitor is phentermine.

In the twenty eighth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is a norepinephrine reuptake inhibitor.

In the twenty ninth embodiment, the invention relates to the composition of the twenty eighth embodiment, wherein said norepinephrine reuptake inhibitor is selected from bupropion, thionisoxetine, and reboxetine.

In the thirtieth embodiment, the invention relates to the composition of the first embodiment, wherein

said second compound is a dopamine agonist.

In the thirty first embodiment, the invention relates to the composition of the thirtieth embodiment, wherein said dopamine agonist is selected from the group consisting of cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine.

In the thirty second embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is a norepinephrine releaser.

In the thirty third embodiment, the invention relates to the composition of the thirty second embodiment, wherein said norepinephrine releaser is diethylpropion.

In the thirty fourth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is a combination of a dopamine reuptake inhibitor and a norepinephrine reuptake inhibitor.

In the thirty fifth embodiment, the invention relates to the composition of the thirty fourth embodiment, wherein said second compound is selected from bupropion and mazindol.

In the thirty sixth embodiment, the invention relates to the composition of the first embodiment, wherein said second compound is a combination of a SSRI and a norepinephrine reuptake inhibitor.

In the thirty seventh embodiment, the invention relates to the composition of the thirty sixth embodiment, wherein said second compound is selected from sibutramine, venlafaxine, and duloxetine.

In the thirty eighth embodiment, the invention relates to the composition of the first embodiment, wherein said first compound is naltrexone and said second compound is fluoxetine.

In the thirty ninth embodiment, the invention relates to the composition of the thirty eighth embodiment, wherein the naltrexone is in a time-release formulation whereas the fluoxetine is in an immediate release formulation.

In the fortieth embodiment, the invention relates to a method of affecting weight loss, comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In the forty first embodiment, the invention relates to the method of the fortieth embodiment, wherein said individual has a body mass index greater than 25.

In the forty second embodiment, the invention relates to the method of the fortieth embodiment, wherein opioid receptor activity is antagonized by administering an opioid receptor antagonist.

In the forty third embodiment, the invention relates to the method of the forty second embodiment, wherein the opioid receptor antagonist is a MOP receptor antagonist.

In the forty fourth embodiment, the invention relates to the method of the fortieth embodiment, wherein the opioid receptor antagonist is selected from alvimopan, norbinaltorphimine, nalmefene, naloxone, naltrexone, methylnaltrexone, and nalorphine, and pharmaceutically acceptable salts or prodrugs thereof.

In the forty fifth embodiment, the invention relates to the method of the forty second embodiment,

wherein said opioid receptor antagonist is a partial opioid agonist.

In the forty sixth embodiment, the invention relates to the method of the forty fifth embodiment, wherein said partial opioid agonist is selected from the group consisting of pentacozine, buprenorphine, nalorphine, propiram, and lofexidine.

In the forty seventh embodiment, the invention relates to the method of the fortieth embodiment through the forty fifth embodiment, wherein .alpha.-MSH activity is enhanced by administering a compound, wherein said compound triggers release of .alpha.-MSH or increases the activity of neurons that express .alpha.-MSH.

In the forty eighth embodiment, the invention relates to the method of the forty seventh embodiment, wherein said compound is a selective serotonin reuptake inhibitor (SSRI) or a specific 5-HT receptor agonist.

In the forty ninth embodiment, the invention relates to the method of the forty eighth embodiment, wherein said 5-HT receptor is selected from 5-HT1b receptor and 5-HT2c receptor.

In the fiftieth embodiment, the invention relates to the method of the forty eighth embodiment, wherein said SSRI is selected from fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, sibutramine, duloxetine, and venlafaxine, and pharmaceutically acceptable salts or prodrugs thereof.

In the fifty first embodiment, the invention relates to the method of the forty seventh embodiment, wherein said compound is a .gamma.-amino butyric acid (GABA) inhibitor.

In the fifty second embodiment, the invention relates to the method of the fifty first embodiment, wherein said GABA inhibitor is a 5-HT1b receptor agonist.

In the fifty third embodiment, the invention relates to the method of the fifty first embodiment, wherein said GABA inhibitor suppresses the expression of the AgRP gene.

In the fifty fourth embodiment, the invention relates to the method of the fifty first embodiment, wherein said GABA inhibitor suppresses the production or release of AgRP.

In the fifty fifth embodiment, the invention relates to the method of the forty eighth embodiment, wherein said 5-HT agonists inhibits the NPY/AgRP/GABA neurons.

In the fifty sixth embodiment, the invention relates to the method of the fifty first embodiment, wherein said GABA inhibitor suppresses the activity of neurons that express AgRP.

In the fifty seventh embodiment, the invention relates to the method of the fifty first embodiment, wherein said GABA inhibitor is topiramate.

In the fifty eighth embodiment, the invention relates to the method of the forty seventh embodiment, wherein said compound is selected from the group consisting of a dopamine reuptake inhibitor, a norepinephrine reuptake inhibitor, a dopamine agonist, a norepinephrine releaser, a combination of a dopamine reuptake inhibitor and a norepinephrine reuptake inhibitor, and a combination of a SSRI and a norepinephrine reuptake inhibitor.

In the fifty ninth embodiment, the invention relates to the method of the fifty eighth embodiment, wherein said compound is not phentermine.

In the sixtieth embodiment, the invention relates to the method of the fortieth embodiment, with the proviso that the individual is not suffering from Prader-Willi syndrome.

In the sixty first embodiment, the invention relates to the method of the fortieth embodiment, with the proviso that if the opioid receptor is antagonized using naltrexone, then release of .alpha.-MSH is not stimulated with fluoxetine.

In the sixty second embodiment, the invention relates to the method of the fortieth embodiment, wherein said treating step comprises administering to said individual a first compound and a second compound, wherein said first compound is an opioid antagonist and said second compound enhances .alpha.-MSH activity.

In the sixty third embodiment, the invention relates to the method of the sixty second embodiment, wherein said first compound and said second compound are administered nearly simultaneously.

In the sixty fourth embodiment, the invention relates to the method of the sixty third embodiment, wherein said first compound is administered prior to said second compound.

In the sixty fifth embodiment, the invention relates to the method of the sixty fourth embodiment, wherein said first compound is administered subsequent to said second compound.

In the sixty sixth embodiment, the invention relates to a method of increasing satiety in an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In the sixty seventh embodiment, the invention relates to the method of the sixty sixth embodiment, wherein said treating step comprises administering to said individual a first compound and a second compound, wherein said first compound is an opioid antagonist and said second compound enhances .alpha.-MSH activity.

In the sixty eighth embodiment, the invention relates to the method of the sixty seventh embodiment, wherein said first compound and said second compound are administered nearly simultaneously.

In the sixty ninth embodiment, the invention relates to the method of the sixty seventh embodiment, wherein said first compound is administered prior to said second compound.

In the seventieth embodiment, the invention relates to the method of the sixty seventh embodiment, wherein said first compound is administered subsequent to said second compound.

In the seventy first embodiment, the invention relates to a method of increasing energy expenditure in an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In the seventy second embodiment, the invention relates to the method of the seventy first embodiment, wherein said treating step comprises administering to said individual a first compound and a second compound, wherein said first compound is an opioid antagonist and said second compound enhances .alpha.-MSH activity.

In the seventy third embodiment, the invention relates to the method of the seventy second embodiment, wherein said first compound and said second compound are administered nearly simultaneously.

In the seventy fourth embodiment, the invention relates to the method of the seventy second embodiment, wherein said first compound is administered prior to said second compound.

In the seventy fifth embodiment, the invention relates to the method of the seventy second embodiment, wherein said first compound is administered subsequent to said second compound.

In the seventy sixth embodiment, the invention relates to a method of suppressing the appetite of an individual comprising identifying an individual in need thereof and treating that individual to antagonize opioid receptor activity and to enhance .alpha.-MSH activity.

In the seventy seventh embodiment, the invention relates to the method of the seventy sixth embodiment, wherein said treating step comprises administering to said individual a first compound and a second compound, wherein said first compound is an opioid antagonist and said second compound enhances .alpha.-MSH activity.

In the seventy eighth embodiment, the invention relates to the method of the seventy seventh embodiment, wherein said first compound and said second compound are administered nearly simultaneously.

In the seventy ninth embodiment, the invention relates to the method of the seventy seventh embodiment, wherein said first compound is administered prior to said second compound.

In the eightieth embodiment, the invention relates to the method of the seventy seventh embodiment, wherein said first compound is administered subsequent to said second compound.

In the eighty first embodiment, the invention relates to a method of affecting weight loss in an individual comprising identifying an individual in need thereof and treating that individual with a combination of naltrexone and fluoxetine,

provided that the individual does not suffer from Prader-Willi syndrome or binge eating disorder.

In the eighty second embodiment, the invention relates to the method of the eighty first embodiment, wherein the individual has a BMI greater than 30.

In the eighty third embodiment, the invention relates to the method of the eighty first embodiment, wherein the individual has a BMI greater than 25.

In the eighty fourth embodiment, the invention relates to the method of the eighty first embodiment, wherein the naltrexone is in a time-release formulation whereas the fluoxetine is in an immediate release formulation.

In the eighty fifth embodiment, the invention relates to the method of the eighty fourth embodiment, wherein the plasma concentration level of both naltrexone and fluoxetine follow a similar concentration profile.

In the eighty sixth embodiment, the invention relates to the method of the eighty fourth embodiment, wherein the naltrexone and the fluoxetine are administered substantially simultaneously.

In the eighty seventh embodiment, the invention relates to the method of the eighty fourth embodiment, wherein the naltrexone is administered prior to the fluoxetine.

In the eighty eighth embodiment, the invention relates to the method of the eighty fourth embodiment, wherein the naltrexone is administered subsequent to the fluoxetine.

EXAMPLES

The examples below are non-limiting and are merely representative of various aspects of the invention.

Example 1

Combination of Fluoxetine and Naltrexone

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take one 20 mg tablet of fluoxetine (PROZAC.RTM.) on a daily basis, in addition to one 50 mg tablet of naltrexone on a daily basis.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

If the initial dosage is not effective, then the fluoxetine dosage can be increased by 20 mg per day, though never exceeding 80 mg total per day. If the initial dosage results in a more rapid weight loss than the above rate, the dosage of each of fluoxetine or naltrexone can be reduced.

Fluoxetine has a physiological half life of about 9 hours, whereas that of naltrexone is about 1.5 hours. Thus, in some cases, it is beneficial to administer one dose of fluoxetine per day in conjunction with two or three or more doses of naltrexone throughout the day. Naltrexone may also be in a time-release formulation where the dose is administered once a day, but naltrexone gradually enters the blood stream throughout the day, or in the course of a 12 hour period.

Example 2

Combination of Fluoxetine and Nalmefene

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take one 20 mg tablet of fluoxetine (PROZAC.RTM.) on a daily basis. In addition, each individual is injected with 1 mL of a solution of 100 .mu.g of nalmefene in 1 mL of saline, intravenously, intramuscularly, or subcutaneously.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

If the initial dosage is not effective, then the fluoxetine dosage can be increased by 20 mg per day, though never exceeding 80 mg total per day. In addition, the dosage of nalmefene may be increased up to 2 mL of a solution of 1 mg of nalmefene in 1 mL of saline. If the initial dosage results in a more rapid weight loss than the above rate, the dosage of each of fluoxetine or nalmefene can be reduced.

Example 3

Combination of Fluoxetine and Naloxone

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take one 20 mg tablet of fluoxetine (PROZAC.RTM.) on a daily basis. In addition, each individual is injected with 1 mL of a solution of 400 .mu.g of naloxone in 1 mL of saline, intravenously, intramuscularly, or subcutaneously.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

If the initial dosage is not effective, then the fluoxetine dosage can be increased by 20 mg per day, though never exceeding 80 mg total per day. If the initial dosage results in a more rapid weight loss than the above rate, the dosage of each of fluoxetine or nalmefene can be reduced.

Example 4

Combination of Opioid Antagonist and Sibutramine

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take nalmefene, naltrexone, or naloxone in the dosage set forth in Examples 1-3. In addition, each individual is instructed to take 10 mg of sibutramine orally once a day.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

If the initial dosage is not effective, then the sibutramine dosage can be increased 15 mg per day. Dosages of sibutramine in excess of 15 mg per day are not recommended. If the initial dosage results in a more rapid weight loss than the above rate, the dosage of each of sibutramine, nalmefene, naltrexone, or naloxone can be reduced.

Example 5

Combination of Opioid Antagonist and Bupropion

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take nalmefene, naltrexone, or naloxone in the dosage set forth in Examples 1-3. In addition, each individual is instructed to take bupropion. The usual adult does is 300 mg per day, given three times daily. Dosing should begin at 200 mg per day, given as 100 mg twice daily. Based on clinical response, this dose may be increased to 300 mg per day, given as 100 mg three times daily. No single dose is to exceed 150 mg.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

Example 6

Combination of Opioid Antagonist and Phentermine

Individuals having a BMI of greater than 25 are identified. Each individual is instructed to take nalmefene, naltrexone, or naloxone in the dosage set forth in Examples 1-3. In addition, each individual is instructed to take 37.5 mg of phentermine orally once a day.

The individuals are monitored for a period of months. It is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

Example 7

Combinations with Naltrexone

In a multicenter, randomized, blinded, placebo-controlled clinical trial with 6 groups, the following drug combinations are tested: Group 1: Fluoxetine 60 mg po QD plus Naltrexone 50 mg po QD Group 2: Fluoxetine 60 mg po QD plus N-placebo po QD Group 3: Bupropion-SR 150 mg po BID plus Naltrexone 50 mg po QD Group 4: Bupropion-SR 150 mg po BID plus N-placebo po QD Group 5: P-placebo po BID plus Naltrexone 50 mg po QD Group 6: P-placebo po BID plus N-placebo po QD

In any of the above groups, the dosage of fluoxetine may be in the range between 6 mg and 60 mg, for example, 6 mg, 10 mg, 12 mg, 18 mg, 20 mg, 24 mg, 30 mg, 36 mg, 40 mg, 42 mg, 45 mg, 48 mg, 54 mg, and 60 mg. Bupropion may be administered in doses in the range between 30 mg and 300 mg, for example, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, and 300 mg. Naltrexone may be administered in doses in the range between 5 mg and 50 mg, for example, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, and 50 mg.

Subjects are evaluated as out-patients during this study. All subjects in this trial receive diet instruction, behavior modification advice and instruction to increase their activity, a regimen shown to give weight loss. Subjects are randomized to receive study drugs in various combinations.

Subjects in groups 5 and 6 cross-over to treatment with fluoxetine plus naltrexone or bupropion SR plus naltrexone after week 16 for the extension treatment period which provide additional data on safety of the combination therapies.

The primary endpoint is percent and absolute change from baseline in body weight at 16 weeks. Secondary endpoints include weight loss at 24, 36, and 48 weeks, number and proportion of subjects who achieve at least a 5% weight loss and a 10% weight loss (responder analysis), changes in obesity-associated cardiovascular risk factors (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose and insulin) and waist circumference, and safety and tolerability. Adverse events, laboratory parameters, vital signs, and the Hospital Anxiety and Depression (HAD) Scale are used to monitor safety and tolerability.

Example 8

Dose-Response Experiments

Seventy, four week old, male C57/B16J.sup.- mice (Jackson Laboratory), 22-30 g were sham injected daily with 0.1 mL 0.9% saline (pH 7.4) for 1 week prior to the experiments. Animals were weighed and randomized to 1 of 7 weight-matched dose groups (0, 1.5, 3, 5.5, 10, 18, and 30 mg/kg; n=10/group for fluoxetine; 0, 1.5, 3, 5.5, 10, 18, and 30 mg/kg; n=3/group for naltrexone) the day before experiments began. Food was removed between 4:30-5:30 pm the day before the experiment. Animals received a 0.3 mL bolus (fluoxetine) or 0.1 mL bolus (naltrexone) intraperitoneal injection between 9-10:30 am, and food was provided immediately following injection. 3 animals/group received injections on each testing day (i.e., 3 runs of 3/group; 1 run of 1/group). Food was weighed 1, 2, 4, 8, and 24 h post-injection. Cumulative food intake.+-.SEM was calculated and analyzed using Prizm. Doses were log transformed and fit to a sigmoidal curve, food intake was expressed as a proportion of the food intake in saline treated animals. From the curve, the EC.sub.50 at each time point for each drug was determined.

Similar procedures as described above were followed using AM251 and nalmefene, fluvoxamine and nalmefene, and bupropion and naltrexone.

The results are set forth in the table below:

TABLE-US-00001 Hour 1 Hour 2 Hour 4 Hour 8 Hour 8 SEM SEM SEM SEM SEM MEAN (.+-.) MEAN (.+-.) MEAN (.+-.) MEAN (.+-.) Saline 1.00 0.0690 1.00 0.062 1.00 0.047 1.00 0.052 1.00 0.042 AM 251 0.97 0.086 0.85 0.060 0.88 0.057 0.90 0.036 0.99 0.054 Fluvoxamine 0.77 0.058 0.85 0.056 0.95 0.044 0.91 0.034 0.92 0.054 Nalmefene 0.0083 0.0062 0.11 0.061 0.57 0.11 0.81 0.068 0.98 0.027 AM 251 + 0.010 0.010 0.075 0.055 0.30 0.1 0.62 0.042 0.90 0.021 Nalmefene Fluvoxamine + 0.0041 0.0041 0.019 0.012 0.42 0.087 0.79 0.026 0.99 0.031 Nalmefene Bupropion 0.32 0.044 0.64 0.049 0.97 0.048 0.96 0.036 0.99 0.020 Naltrexone 0.41 0.040 0.77 0.060 0.99 0.062 1.1 0.048 0.98 0.030 Naltrexone + 0.042 0.0068 0.34 0.10 0.89 0.055 0.97 0.044 0.95 0.028 Bupropion Naltrexone 0.30 0.10 0.56 0.050 0.83 0.10 0.98 0.19 1.01 0.22 Fluoxetine 0.36 0.030 0.57 0.13 0.68 0.15 0.76 0.21 1.05 0.22 Naltrexone + 0.070 0.030 0.26 0.060 0.72 0.11 0.95 0.18 1.04 0.26 Fluoxetine

Example 9

Electrophysiology Data

To test the hypothesis that drugs selectively activate POMC neurons, we used a strain of transgenic mice expressing green fluorescent protein (EGFP, Clontech), under the transcriptional control of mouse Pomc genomic sequences that include a region located between -13 kb and -2 kb required for accurate neuronal expression Bright green fluorescence (509 nm) was seen in the two CNS regions where POMC is produced: the ARC and the nucleus of the solitary tract. Under ultraviolet (450-480 nm) excitation, POMC neurons were clearly distinguished from adjacent, non-fluorescent neurons visualized under infrared optics.

200 .mu.m thick coronal slices were cut from the ARC of four-week old male POMC-EGFP mice. Slices were maintained in Krebs solution (NaCl (126 mM), KCl (2.5 mM), MgCl.sub.2 91.2 mM), CaCl.sub.2.2H.sub.2O (2.4 mM), NaH.sub.2PO.sub.4.H.sub.2O (1.2 mM), NaHCO.sub.3 (21.4 mM), glucose (11.1 mM)) at 35.degree. C. and saturated with 95% O.sub.2 and 5% CO.sub.2 for 1 hr prior to recordings. Recordings were made in Krebs at 35.degree. C. Slices were visualized on an Axioskop FS2 plus (Zeiss) through standard infra red optics and using epifluorescence through a FITC (longpass) filter set. POMC-EGFP neurons in hypothalamic slices had a resting membrane potential of -40 to -45 mV and exhibited frequent spontaneous action potentials. Cell-attached recordings were made from fluorescent neurons using an Axopatch 200B amplifier (Axon Instruments) and Clampex 8 (Axon Instruments). Action potentials frequencies were determined using an event detection program (Mini Analysis; Synaptosoft Inc., Decatur, Ga.). Drugs were applied to the bath for 3 min.

Data were analyzed by determining the average firing rate for 500 sec prior to drug addition, and analyzing treatments relative to this frequency (that is, firing rates were normalized to the pre-treatment frequency). The ratio's listed for the combinations are the ratio of the effect of naltrexone in combination with the POMC activator, relative to naltrexone alone (that is the extra effectiveness that naltrexone conferred to the POMC activator). Also listed are the mean effects of the drugs alone.

TABLE-US-00002 Fenfluramine 2X increase (n = 6) Fenfluramine + Naltrexone 5.2X (n = 8) Fluoxetine 3X (n = 1) Fluoxetine + Naltrexone 1.2X (n = 1) Dopamine 11X (n = 9) Dopamine + Naltrexone 1.5X (n = 3)

Naltrexone alone has a potent (7.times.) but variable effect. many cells did not respond to naltrexone alone, but gave a significant response to combination treatment. Heisler et al. (Science 297(5581):609-11 (2002)) show that fenfluramine alone causes a 200% effect.

The results are set forth in the table below:

TABLE-US-00003 Drug Dose Effect (%) Drug Dose Effect (%) Ratio Naltrexone 1 .mu.M 29650 Naltrexone + 1 .mu.M + 20 .mu.M 15080 0.51 Fenfluramine Naltrexone 1 .mu.M 2200 Naltrexone + 1 .mu.M + 20 .mu.M 11440 520 Fenfluramine Naltrexone 1 .mu.M 2500 Naltrexone + 1 .mu.M + 20 .mu.M 856 0.34 Fenfluramine Naltrexone 1 .mu.M 417 Naltrexone + 1 .mu.M + 20 .mu.M 5700 13.67 Fenfluramine Naltrexone 1 .mu.M 177 Naltrexone + 1 .mu.M + 20 .mu.M 430 2.43 Fenfluramine Naltrexone 1 .mu.M 200 Naltrexone + 1 .mu.M + 20 .mu.M 2933 14.67 Fenfluramine Naltrexone 1 .mu.M 700 Naltrexone + 1 .mu.M + 20 .mu.M Fenfluramine Naltrexone 1 .mu.M 900 Naltrexone + 1 .mu.M + 20 .mu.M 1831 2.03 Fenfluramine Naltrexone 1 .mu.M 2273 Naltrexone + 1 .mu.M + 20 .mu.M Fenfluramine Naltrexone 1 .mu.M 300 Naltrexone + 1 .mu.M + 20 .mu.M 920 3.07 Fenfluramine

* * * * *

United States Patent **7,256,202**
Halow **August 14, 2007**

Composition and method for treatment of hepatic encephalopathy

Abstract

The inventions provide an improved treatment for hepatic encephalopathy characterized by hyperammonemia and/or constipation, comprising the oral administration of polyethylene glycol (PEG) in amounts sufficient to reduce plasma levels of ammonia and/or to alleviate constipation. Preferably, the PEG is administered in combination with lactulose, which provides a palatable composition for the treatment of HE with excellent therapeutic benefits and reduced side effects as compared to lactulose alone.

Inventors: **Halow; George M.** (El Paso, TX)
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Primary Examiner: Kwon; Brian
Attorney, Agent or Firm: Hoffman, Wasson & Gitler Buttmi; Jean A.

Claims

What is claimed is:

1. A method for the treatment of a patient with hyperammonemia, comprising orally administering to the patient a pharmaceutical composition free of serum electrolytes and comprising from about 0.15 to 3.5 parts by weight polyethylene glycol (PEG) to about 1 part by weight lactulose, in an amount and frequency sufficient to reduce patient plasma ammonia to a clinically-acceptable level or to maintain this level, or both.

2. The method of claim 1, wherein the composition is a dry composition formulated as a liquid drink by admixture with a pharmaceutically-acceptable aqueous carrier.

3. The method of claim 1, wherein the composition comprises from about 0.5 to 3 parts by weight PEG to 1 part by weight lactulose.

4. The method of claim 2, wherein the composition is administered in single dosages each comprising about 5 to 35 gm of dry PEG dissolved in the aqueous carrier.

5. The method of claim 4, wherein each single dosage further comprises about 10 to 30 gm of dry lactulose dissolved in the aqueous carrier.

6. The method of claim 5, wherein each single dosage comprises about 10 to 20 gm PEG and about 10 to 20 gm lactulose dissolved in the aqueous carrier.

7. The method of claim 1, wherein the PEG is solid at room temperature.

8. The method of claim 4, wherein the composition is administered on a continuing basis in at least one single dosage per day.

9. The method of claim 5, wherein the composition is administered on a continuing basis in at least one single dosage per day.

10. The method of claim 6, wherein the composition is administered on a continuing basis in at least one single dosage per day.

11. The method of claim 8, wherein the composition is administered on a continuing basis of once or twice a day.

12. The method of claim 9, wherein the composition is administered on a continuing basis of once or twice a day.

13. The method of claim 10, wherein the composition is administered on a continuing basis of once or twice a day.

14. The method of claim 3, wherein the composition is a dry composition formulated as a liquid drink by admixture with a pharmaceutically-acceptable aqueous carrier.

15. The method of claim 14, wherein the composition is administered in single dosages each comprising about 5 to 35 gm of dry PEG dissolved in the aqueous carrier.

16. The method of claim 15, wherein each single dosage further comprises about 10 to 30 gm of dry lactulose dissolved in the aqueous carrier.

17. The method of claim 16, wherein each single dosage comprises about 10 to 20 gm PEG and about 10 to 20 gm lactulose.

18. The method of claim 15, wherein the composition is administered on a continuing basis in at least one single dosage per day.

19. The method of claim 16, wherein the composition is administered on a continuing basis in at least one single dosage per day.

20. The method of claim 17, wherein the composition is administered on a continuing basis in at least one single dosage per day.

21. The method of claim 18, wherein the composition is administered on a continuing basis of once or twice a day.

22. The method of claim 19, wherein the composition is administered on a continuing basis of once or twice a day.

23. The method of claim 20, wherein the composition is administered on a continuing basis of once or twice a day.

24. The method of claim 3, wherein PEG is a solid at room temperature.

Description

BACKGROUND OF THE INVENTION

1. Field of Art

Hepatic encephalopathy (HE) is a syndrome associated with liver dysfunction, characterized by a decline in mental function and neurological abnormalities. Distinctive clinical signs include personality changes and intellectual impairment, and neuromuscular anomalies such as asterixis (flapping tremor) and alterations in gait.

The syndrome typically manifests in patients with an extensive collateral blood vessel system (extrahepatic portal shunts) which diverts portal venous blood away from the liver into the systemic circulation. Thus, toxic metabolites absorbed into the bloodstream from the intestines may largely bypass the liver and enter the general circulatory system without being detoxified. Among other ramifications, such toxins can cause metabolic aberrations in the central nervous system (CNS) which lead to increased permeability of the blood-brain barrier and increased transport of toxic substances across this barrier into the brain. In addition to promoting permeability of the neuronal membrane, high plasma levels of certain neurotoxins are thought to contribute to changes in energy metabolism and nerve processes in the brain. Neurotoxins which have been implicated in the pathogenesis of hepatic encephalopathy include false neurotransmitters, mercaptans, .gamma.-amino butyric acid, and ammonia.

Ammonia is normally produced in the gastrointestinal tract by bacterial degradation of peptides and other nitrogen-containing compounds, and then detoxified in the liver by conversion to urea and glutamine. If the liver is sufficiently diseased, or bypassed as when portal shunts are present, plasma levels of ammonia may increase to toxic levels, affecting, for example, the transport of amines, water, and electrolytes across the neuronal membrane. While the role that ammonia plays in the pathogenesis of hepatic encephalopathy is not entirely clear, reduction of plasma levels of ammonia has been clinically observed to improve HE in many cases, and evaluation of ammonia blood levels for hyperammonemia is widely routine in suspected cases.

2. Discussion of Related Art

A common treatment of hyperammonemia in hepatic encephalopathy is the oral administration of lactulose, a disaccharide of fructose and galactose. Lactulose is not metabolized by mammals and reaches the large intestine substantially intact, where it is digested by resident microorganisms to produce organic acids (lactic, formic, acetic) and CO.sub.2. High local concentrations of lactulose draw free ammonia in solution from the bloodstream into the bowel where it reacts with these acids to form their ammonium salts which are then excreted.

In addition to ammonia detoxification in HE, lactulose additionally functions as an osmotic laxative or stool softener by increasing gut solute concentrations and drawing water into the large intestine. As constipation as well as hyperammonemia is a common condition in HE, lactulose is a significant therapy for patients. However, it is very difficult to obtain compliance from patients for several reasons, mainly that current lactulose formulations have a very bad taste, and that at the required dosages they frequently cause bloating and nausea to the point of significant discomfort.

SUMMARY OF THE DISCLOSURE

The inventions provide an improved treatment for hepatic encephalopathy characterized by hyperammonemia and/or constipation, comprising the oral administration of polyethylene glycol (PEG) in amounts sufficient to reduce plasma levels of ammonia and/or to alleviate constipation. Preferably, the PEG is administered in combination with lactulose, which provides a palatable composition for the treatment of HE with excellent therapeutic benefits and reduced side effects as compared to lactulose alone.

DETAILED DESCRIPTION OF THE INVENTIONS

As described at length in U.S. Pat. No. 5,710,183 issued 20 Jan. 1998 to the present inventor, PEG has been used as an osmotic bowel cleanser or laxative which draws water into the bowel, thereby increasing bowel motility and softening the stool. The present inventions are predicated on the discovery that the osmotic effects of PEG are useful not only for softening the stool and/or increasing bowel motility of constipated HE patients, but also for inhibiting production of ammonia in the bowel of patients at risk of hyperammonemia by accelerating the passage of proteins and other nitrogenous metabolites through the gastrointestinal tract. By reducing the residence time of ingested food in the digestive system, catabolism of metabolites yielding ammonia byproduct is minimized. The residence time can be managed by adjusting the PEG dosage for the desired results; if, for example, a dietary overload of protein has precipitated or exacerbated an occurrence of HE, higher and/or more frequent dosages of PEG which will induce at least moderate diarrhea to minimize protein digestion and the consequent production of ammonia, may be desirable. In severe cases, one may want to use amounts of PEG suitable for bowel cleansing, for example as set forth in U.S. Pat. No. 5,710,183, incorporated herein by reference.

In a preferred embodiment, the invention comprises a composition of PEG and lactulose powder for the treatment of constipation and/or hyperammonemia in HE or other needy patients. This composition combines the osmotic properties of lactulose and PEG for laxative/stool softening benefits; additionally, these same osmotic properties increase the fluid volume in the gut by drawing in liquid containing excess free ammonia, which facilitates conversion of this toxin to harmless ammonium salts in the presence of endogenous bacteria and lactulose as detailed supra. Thus, lactulose both enhances the osmotic properties of the PEG and mediates detoxification of ammonia entering the intestine by osmosis. Further, the gas and cramping which frequently occurs with the use of lactulose alone for treating HE is significantly reduced, owing in part to the significantly lower dosage (1/2 to 1/3 the standard dose) used herein. Importantly, compositions of the invention containing both lactulose and PEG are effective in low volume, low frequency dosages and are also surprisingly palatable so that patients are far more compliant with their treatment regimens and results are significantly improved.

Polyethylene glycols useful in the composition of the invention broadly comprise any food-grade or pharmaceutical-grade PEG. Currently preferred for convenience of use in preparing and using the composition of the invention are polymers having molecular weights above about 900 which are solid at room temperature and soluble in or miscible with water. Polymers having average molecular weights between about 3000 and 8000 are exemplary; PEG 4000, which is nearly odorless and tasteless and

widely available in USP grade, or PEG 3350, are very suitable. These and other suitable PEG powders are commercially available, from, for example, Spectrum Chemical Mfg. Company, Gardena, Calif. A proprietary laxative, MiraLax.RTM. (Braintree Laboratories, Braintree, Mass.) is a useful source of PEG 3350 powder readily soluble in water. Non-powdered PEG should be comminuted to a particle size that is readily soluble/miscible in water before use. Lower molecular weight polymers such as PEG 400 which are liquid at room temperature may also be used in the practice of the invention, however, they are not generally expected to be as satisfactory as higher molecular weight PEGs. PEG compositions without added electrolytes such as found in Colyte.RTM. (Schwartz Pharma, Milwaukee) and other proprietary PEG-based bowel lavages, are preferred for their better taste.

Lactulose for the practice of the invention is readily available over-the-counter. A convenient and relatively tasteless formulation, often referred to in the trade as "lactulose powder for oral solution" can be obtained, for example, from Bertek Pharmaceuticals, Sugarland, Tex. as Kristalose.RTM. in 10 and 20 gm packets. The lactulose syrups commonly sold as laxatives such as Cephulac.RTM., Chronulac.RTM., Cholac.RTM., and Enulose.RTM. are not preferred in the practice of the present inventions as several contain undesirable additives and many patients object to their taste. However, such syrups can be substituted for lactulose powder by using sufficient syrup to provide the desired dosage of lactulose; typically, the named syrups contain about 10 gm lactulose in 15 ml of syrup.

PEG and lactulose are each prepared as described above, conveniently as powders, for ready solubility/dispersability in water or other aqueous liquid such as juice to provide a palatable drink for liquid administration. If a PEG/lactulose composition is desired, the powders are then combined to form a dry composition and, for use, dissolved in the selected liquid. The PEG and lactulose components are typically combined in proportions of from about 0.15 to 3.5 parts by weight PEG to 1 part by weight lactulose; in many cases, a range of from about 0.5 to 2 or 0.5 to 3 parts by weight of PEG to 1 part by weight lactulose will be effective. If the PEG to lactulose ratio is too low, the side effects of the lactulose will become pronounced and compliance will drop off; if the PEG to lactulose ratio is too high, the volume of composition which must be ingested to obtain the benefits of the lactulose component may be undesirably high and the excess of PEG may exacerbate or precipitate undesirable side effects. Individual dosages will usually range from about 5 to 35 gm PEG and from about 10 to 30 gm lactulose powder (or more if it is indicated and can be tolerated). In mild-to-moderate or moderately severe cases of HE from about 10 to 20 gm PEG to about 10 to 20 gm lactulose is recommended as a starting dosage. In a particular example, about 10 gm powdered lactulose such as Kristalose.RTM. is admixed with about 17 gm powdered PEG 3350 (Spectrum Chemical Mfg. Company, Gardenia, Calif.) to provide a dry lactulose/dry PEG composition according to the invention comprising 1.7 parts by weight PEG to 1 part by weight lactulose, to be taken diluted with water or other water-based liquid to taste.

For use, the dry lactulose/dry PEG composition, with or without optional conventional additives such as electrolytes coloring matter, or flavorings, is dispersed/dissolved in sufficient water or other aqueous medium to formulate a relatively smooth, palatable drink. Single dosages of dry composition containing from about 5 to 35 gm of PEG, for example, about 17 gm, admixed with about 10 to 30 gm lactulose, for example about 10 gm, are conveniently dispersed/dissolved in from about 6 to 10 fl. oz., conveniently about 8 fl. oz., of water or other palatable water-based liquid such as juice, to provide a low-volume drink for oral administration. About two tablespoons of a dry lactulose/PEG composition according to the invention dissolved in about 8 fl. oz. of water and administered from about 1 to 3 times a day, usually 2 times a day, will generally provide satisfactory results. The volume of water or other liquid in which the dry composition is dissolved/dispersed is not critical; in fact, two to three or more extra glasses of water or other liquid in conjunction with each drink may be generally beneficial. The dosages can be administered once or twice a day or more if indicated (e.g., tid or qid) until HE symptoms have abated. Results achieved include alleviation of constipation with bowel movements from 2-4 times per day and reduction of toxic plasma ammonia levels by about 25% to 50% or more to clinically-acceptable

stable levels.

The product has a relatively rapid response time of from one to about two days. A maximum response can be expected in from one to two weeks, with the response continuing on this plateau with continued use of the product. The product is not habit forming, and can be administered as needed or on a continuing basis for many weeks, months, or years, usually without significant problem. Dosages can be increased or decreased, or PEG or lactulose concentration increased or decreased to modulate results according to medical necessity. For example, moderate to heavy diarrhea may be initially desirable if, for example, HE has been precipitated by excessive protein intake, to flush nitrogenous compounds from the bowel before they are degraded to ammonia: in this case, an increase in the number of dosages per day may be helpful as may be an increase in PEG concentration in the dosage formulation, or both. Conversely, if for example, constipation has been substantially alleviated but ammonia levels remain undesirably high, an increase in the lactulose concentration of the dosage formulation may be helpful. In some cases, such as severe HE requiring hospitalization, it may be desirable to administer the PEG dosage separately from the lactulose dosage, as by alternating the selected amount of lactulose with the selected amount of PEG two or more times daily.

In an alternate mode of practice according to the invention, powdered lactulose may be combined with liquid PEG (polyethylene glycol polymer which is liquid at room temperature) or dissolved powdered PEG. Proportions for a suitable liquid PEG/lactulose composition comprise, for example, about 10 to 20 gms powdered lactulose in 8-10 fl. oz. of PEG. If desired, the liquid PEG/lactulose composition may be further diluted with water for oral administration; for this application, PEG soluble in or miscible with water at room temperature is much preferred. Diluted or undiluted, the liquid or liquified PEG/lactulose composition is conveniently administered orally, in a regimen as described above for a diluted dry lactulose PEG composition. The liquid compositions of lactulose syrup and PEG powder mentioned above can be similarly prepared, admixing for example from about 15 to 30 ml syrup containing 10 g lactulose/15 ml of syrup with from about 10 to 20 gm powdered PEG; this composition may also be diluted as desired for oral administration as described above. If desired, a suitable wetting agent is added to any of the liquid lactulose/PEG compositions to promote dispersal/dissolving of the dry matter in the liquid to make a reasonably smooth and palatable drink.

As previously noted, PEG in either powdered or liquid form can be efficacious alone, particularly in milder cases of HE. In this mode of practicing the invention, individual dosages of PEG in amounts of from about 5 to 35 gm, especially from 10 to 20 gm, powder or from about 8-10 fl. oz. liquid are administered to HE patients whose plasma ammonia levels require reduction, in amounts sufficient to effect this reduction in the regimens described supra for PEG/lactulose compositions, e.g., 1 to 3 times daily.

In practice the inventions described herein can provided a good clinical response with substantial resolution of both cognitive and physical symptoms of HE such as confusion and asterixis. Importantly, the inventions permit HE patients in many cases to maintain themselves on a restricted protein diet (30-40 g protein daily), without significant recurrence of HE.

The following Examples are illustrative of making, using, and practicing the invention.

EXAMPLE

The patient is a 78 year old female with cryptogenic cirrhosis, a type of cirrhosis which has unknown etiology. She has had extensive workups for chronic anemia in one of the major California hospitals and was placed on neomycin, Lasix, iron sulfate, lactulose, and Prevacid; she also was on a restricted protein diet to reduce ammonia production. She had intermittent episodes of hepatic encephalopathy during her

hospitalization. The patient's hemoglobin slowly drops and she requires transfusions periodically because of portal gastropathy. The patient's ammonia levels are high, for which she takes lactulose up to three to four times a day; she has three to four to five bowel movements per day. The patient has a difficult time taking lactulose because of the nausea, abdominal discomfort, and bloating sensation she gets with the drug and its unpleasant taste. Although the therapeutic range is three to four bowel movements per day, it is very difficult for her to get to that range because of these effects.

The patient has required several hospitalizations for lethargy, declines in hemoglobin, and hepatic encephalopathy. She has intermittent episodes of abdominal discomfort and mild irritation of various small bowel loops.

Laboratory data shows creatinine at 1.5, albumin at 2.6, total bilirubin at 1.17, and hemoglobin in the 9 to 10-range constantly declining and requiring transfusions periodically. The platelet count is in the range of 57,000. The lowest level of ammonia has been 30 micromoles/L and several levels have been 80 to 90 micromoles/L with the patient taking the lactulose.

The patient has had three hospitalizations for hepatic encephalopathy and anemia, mostly resulting from poor compliance. The patient's last hospitalization was July 22nd. Four months later, the patient presented us with hepatic encephalopathy and bedsores.

She was switched to 17 g MiraLax.RTM. (PEG 3350 powder) combined with 10 g of lactulose dissolved in water and given twice a day. The patient's ammonia level is now in the 70 to 75-range of micromoles/L and holding fairly steady on a maintenance dosage of this composition once per day.

The patient is now alert and oriented with no tremor or asterixis or any signs of hepatic encephalopathy. The patient is more compliant and accepts the taste and does not get the bloating and nausea and crampy sensations associated with lactulose. She has achieved clinical and therapeutic levels of ammonia levels, and is oriented to time and place, with no clinical signs of hepatic encephalopathy on physical examination.

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United States Patent **7,273,889**
Mermelstein , et al. **September 25, 2007**

NMDA receptor antagonist formulation with reduced neurotoxicity

Abstract

The present invention is directed to pharmaceutical compositions of effective amounts of NMDA receptor antagonists and preservative for the administration to a patient in need of effective analgesia and anesthesia. The compositions of the invention advantageously do not cause any significant neurotoxicity. The preferred NMDA receptor antagonist is ketamine. The preferred preservative is benzalkonium chloride.

Inventors: **Mermelstein; Fred H.** (Upper Montclair, NJ), **Albin; Randi** (North Bergen, NJ)
Assignee: **Innovative Drug Delivery Systems, Inc.** (New York, NY)
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Primary Examiner: Kwon; Brian
Attorney, Agent or Firm: Baker Botts L.L.P.

Claims

What is claimed is:

1. A pharmaceutical composition which comprises an aqueous solution containing about 10% ketamine hydrochloride and about 0.002% benzalkonium chloride, wherein the composition does not cause any significant neurotoxicity, and wherein the level of neurotoxicity is comparable to sterile water when administered.

2. The pharmaceutical composition of claim 1, further comprising a suitable carrier selected from the group consisting of water, saline, bicarbonate, sucrose and mixtures thereof.

3. A pharmaceutical composition which comprises an aqueous solution containing about 10% ketamine hydrochloride and about 0.001% to about 0.2% benzalkonium chloride, wherein the composition does not cause any significant neurotoxicity, and wherein the level of neurotoxicity is comparable to sterile water when administered.

4. A pharmaceutical composition which comprises an aqueous solution containing about 0.01 mg/kg to about 1 mg/kg ketamine hydrochloride and about 0.00 1% to about 0.2% per unit dose benzalkonium chloride, wherein the composition does not cause any significant neurotoxicity, and wherein the level of neurotoxicity is comparable to sterile water when administered.

Description

FIELD OF THE INVENTION

The present invention is directed to reducing toxicity of an NMDA receptor antagonist formulation. In particular, the invention is directed to an NMDA receptor antagonist composition which is administered

for its analgesic and anesthetic effects, and which avoids significant neurotoxic side effects.

BACKGROUND OF THE INVENTION

An NMDA receptor is a postsynaptic, ionotropic receptor that is responsive to, inter alia, the excitatory amino acids glutamate and glycine and the synthetic compound NMDA. The NMDA receptor controls the flow of both divalent and monovalent ions into the postsynaptic neural cell through a receptor associated channel (Foster et al., Nature 1987, 329:395-396; Mayer et al., Trends in Pharmacol. Sci. 1990, 11:254-260). Activation of the NMDA receptor has been shown to be the central event which leads to excitotoxicity and neuronal death in many disease states, as well as a result of hypoxia and ischemia following head trauma, stroke and following cardiac arrest. The NMDA receptor has been implicated during development in specifying neuronal architecture and synaptic connectivity, and may be involved in experience-dependent synaptic modifications. In addition, NMDA receptors are also thought to be involved in long term potentiation and central nervous system disorders.

It is known in the art that the NMDA receptor plays a major role in the synaptic plasticity that underlies many higher cognitive functions, such as memory acquisition, retention and learning, as well as in certain nociceptive pathways and in the perception of pain (Collingridge et al., The NMDA Receptor, Oxford University Press, 1994). In addition, certain properties of NMDA receptors suggest that they may be involved in the information-processing in the brain that underlies consciousness itself.

NMDA receptor antagonists are therapeutically valuable for a number of reasons. In addition to anesthesia, certain NMDA receptor antagonists confer profound analgesia, a highly desirable component of general anesthesia and sedation. Also, NMDA receptor antagonists are neuroprotective under many clinically relevant circumstances (including neuropathic pain states, ischemia, brain trauma, and certain types of convulsions).

However, it is clear from the prior art that there are a number of drawbacks associated with current NMDA receptor antagonists. These include the production of involuntary movements, stimulation of the sympathetic nervous system, induction of neurotoxicity at high doses (which is pertinent since NMDA receptor antagonists have low potencies as general anesthetics), depression of the myocardium, and proconvulsions in some epileptogenic paradigms, e.g., "kindling" (Wlaz et al., Eur. J. Neurosci. 1994; 6:1710-1719). There have been considerable difficulties in developing new NMDA receptor antagonists that are able to cross the blood-brain barrier, which results in higher effective dosage requirements.

Commercially available NMDA antagonists have a wide variety of uses. For example, memantine provides rapid and enduring improvement in cognitive, psychological, social and motor impairments of dementia; dextromethorphan is used to relieve coughs; amantadine is an antiviral substance; and ketamine as an anesthetic agent. Certain opioids such as methadone, dextropropoxyphene, and ketobemidone are also classified as NMDA antagonists. MK-801 (dizocilpine maleate) and phencyclidine are not commercially used, and dextrophan, which is used commercially are other examples. However, a level of toxicity which accompanies these antagonists has proven to be problematic.

There are numerous potential commercial applications for NMDA antagonist formulations without neurotoxicity in supervised medical practice. Indications include, but are not limited to, treatment of dementia, suppression of cough (antitussive), antiviral treatment, treatment of involuntary muscle actions, antidepressant, suppression of addiction, and treatment of withdrawal. Ketamine, for example, can be used as an analgesic for breakthrough pain, anesthesia and sedation. Additional indications for ketamine include traumatic orthopedic injury pain, migraine pain, obstetrical use for end-stage labor pain, central pain, dental pain, and a host of additional conditions associated with acute and chronic,

moderate to severe pain.

More specifically, ketamine, an NMDA receptor antagonist, has been in clinical use for over twenty-five years as a dissociative anesthetic and has demonstrated a wide margin of safety when used acutely as an anesthetic agent. Studies demonstrate the analgesic efficacy of ketamine in a variety of diverse indications including patient self-management of pain (U.S. Pat. Nos. 6,248,789 and No. 5,543,434 to Weg), post-operative analgesia (Naguib et al., Can. Anaesth. Soc. J. 1986, 33:16; Dich-Nielsen et al., Acta Anaesthesiol. Scand. 1992, 36:583; Battacharya et al., Ann. Acad. Med. Singapore 1994, 23:456), analgesia in emergency settings for patients suffering from fractures and soft tissue injury (Hirlinger and Pfenninger, Anaesthsist 1987, 36:140), musculoskeletal trauma (Gurnani et al., Anaesth. Intens. Care 1996, 24:32), wound care procedures (Bookwalter, Plastic Surg. Nursing 1994, 14:43; Humphries et al., J. Burn Care Rehabil. 1997, 18:34), management of acute episodes of neuropathic pain attributed to post-herpetic neuralgia (Eide et al., Pain 1994, 58:347), phantom limb pain (Knox et al., Anaesth. Intens. Care 1995, 23:620), nociceptive orofacial pain (Mathisen et al., Pain 1995, 61:215), and cancer pain (Mercadante et al., J. Pain Symptom Manage. 1995, 10:564; Clark and Kalan, J. Pain Symptom. Manage. 1995, 10:310; Fine, J. Pain Symptom Manage. 1999, 17:296; Lauretti et al., Anesthesiology 1999, 90:1528). These studies describe the use of ketamine administered by a variety of routes including transnasal, parenteral, and oral.

There are conflicting results from studies evaluating the potential for ketamine to cause neurotoxicity. Early in vitro studies examining the morphologic changes in cultured cells incubated with ketamine demonstrated that the drug induced, to a varied extent, damage of the myelin sheath and degeneration of mitochondria into multilamellar bodies in organotypic spinal cord slices derived from fetal rats (Shahar et al., Neurochem. Res. 1989, 14:1017). These apparent cytotoxic effects of ketamine were both dose-related and reversible. While no neurotoxic effects of ketamine have been observed in primates or rabbits, spinal cord lesions have been reported in rats and monkeys (Ahuja, Br. J. Anaesth. 1983, 55:991; Malinovsky et al., Anesthesiology 1991, 75:91; Gebhardt, Anaesthesist 1994, 43(suppl.2):S34). In addition, there is evidence of post-mortem histopathologic changes of subpial spinal cord vacuolation in a terminally ill cancer patient who received a continuous infusion of intrathecal ketamine at a rate of 5 mg/day for a duration of three weeks (Karpinski et al., Pain 1997, 73:103). Based on this finding, it was concluded that intrathecal ketamine may cause vacuolar myelopathy and that local vacuolation may be related to the lipophilicity of the drug. In addition, other studies have found that NMDA receptor antagonists, as phencycladine, MK-801, tiletamine, and ketamine cause neuronal vacuolization (Olney et al., Science 1989, 244:1360).

The studies describing the potential neurotoxic effects of ketamine are largely confined to administration of the drug by the intrathecal, or subarachnoid, route. Intrathecal administration of drugs may produce toxic reactions such as demyelination, arrachnoditis, and vascular changes and necrosis.

According to standard practice, ketamine is usually employed containing a preservative. Studies comparing the neurotoxicologic profile of preservative-free ketamine to ketamine containing preservative (chlorobutanol or benzethonium chloride) yielded curious results. Experiments with baboons, monkeys, rabbits, and rats receiving between 0.2 and 50 mg intrathecal ketamine with and without preservative failed to demonstrate histopathologic central nervous system lesions attributable to the drug, but nonetheless detected a breach of the blood brain barrier that was attributable to the presence of preservative (Malinovsky et al., Anesthesiology 1993, 78:109; Karpinski et al., Pain 1997, 73:103). The results were surprising since the combination of a drug with a preservative may also cause, or exacerbate, neurological damage due to the preservative itself (Brock-Utne et al., S.A. Med. J. 1982, 20:440). A further comparative study of multiple dose intrathecally administered preservative-free ketamine, ketamine containing the preservative benzethonium chloride, and benzethonium chloride alone was performed in an attempt to resolve the apparent discrepancies in the animal models (Errando

et al., Reg. Anesth and Pain Med. 1999, 24:146). The results of this analysis demonstrated that preservative-free ketamine was without neurotoxic effect. However, ketamine with preservative produced minor changes to the spinal cord of the animals, and benzethonium chloride alone produced moderate neurotoxic effects (Errando et al., Reg. Anesth and Pain Med. 1999, 24:146). The results of this study confirm the lack of apparent independent neurotoxicity of ketamine and support the view that preservative-free ketamine is safe for intrathecal use in humans, even for repeated injections.

This observation was of limited value, however, since, while single-dose preparations may not require preservatives, other substances require the addition of preservatives to prevent or inhibit microbial growth and avoid spoilage of the preparation. Benzethonium chloride, a quaternary ammonium salt, is a common preservative similar to other cationic surfactants. The animal models, noted previously, indicated that the accompanying preservative, benzethonium chloride, and not ketamine itself, is the likely culprit mediating neurotoxicity in the anesthetic formulation following intrathecal administration of the drugs. With the known neurotoxic effects of this class of preservative, there remains a need in the art for a safe and effective analgesic and anesthetic formulation. The present invention addresses this need with a unique formulation which inhibits or diminishes the neurotoxicity.

SUMMARY OF THE INVENTION

It has now been discovered that benzalkonium quaternary ammonium compounds can be effectively used as preservatives for NMDA receptor antagonists which achieve the desired analgesic and anesthetic effects, without neurotoxic side effects. This discovery runs contrary to evidence of neurotoxicity associated with the administration of NMDA receptor antagonists or antagonists with preservative. Thus, the invention provides greater safety of prepared NMDA receptor antagonist formulations, which avoids the need to prepare preservative-free solutions before every use.

The invention addresses the need in the art for effective preservatives which have no observable propensity to cause neurotoxicity, such as neuron vacuolation or degeneration. The discovery is particularly surprising in that the benzalkonium compound is of the same class of compounds as the benzethonium compound which, as described above, has demonstrated neurotoxic side effects. Both are benzyl quaternary compounds, which are cationic surfactants.

A particularly preferred NMDA receptor antagonist for use in the invention is ketamine. A preferred benzalkonium compound is benzalkonium chloride.

DETAILED DESCRIPTION

The present invention provides a formulation comprising a preservative selected from the benzalkonium chloride quaternary ammonium salts, and a therapeutically effective dose of an NMDA receptor antagonist, i.e., a dose effective to alleviate pain. The invention avoids the neurotoxicity of other preservatives and provides a formulation with reduced or close to no neurotoxicity. The composition is administered for the analgesic or anesthetic effects without causing any significant neurotoxic side effects.

The use of intranasal ketamine has been studied as a safe and effective treatment for patients suffering from breakthrough pain. Because breakthrough pain can occur in chronic pain conditions, such as cancer, consideration was given to the possibility of neurotoxicity of transnasal ketamine compositions containing benzethonium chloride. The present invention is based on the discovery that ketamine formulations, as studied in rats, containing benzalkonium chloride as a preservative demonstrated no observable effects in neuron vacuolation or degeneration.

The present invention addresses the need in the art for pharmaceutical compositions comprising an NMDA receptor antagonist with an effective preservative having reduced neurotoxicity. Benzalkonium chloride is used at relatively low concentrations (0.001-0.02%) and has optimal activity when pH is greater than 4, and at a pH up to 10, is stable at room temperature. Benzalkonium chloride is widely used as a preservative in commercial nasal sprays. Nasal irritation has been associated with chronic use of certain nasal products, and there have been isolated reports of the ability of benzalkonium chloride to cause irritation to the nasal mucosa. However, there appears to be no effect at the concentration intended for use in the present invention's formulation (Kuboyama et al., J. Toxicol. Sci.1997, 22:153).

The NMDA receptor antagonists used in the invention include, but are not limited to ketamine, dextromethorphane, dextrophan, methadone, dextropropoxyphene, ketobemidone, and phencycladine. In the preferred embodiment, the NMDA receptor antagonist is ketamine.

Other examples of antagonists include competitive and non-competitive antagonists. The competitive NMDA antagonists include 2-amino-7-phosphonoheptanoic acid (AP 7) and analogs; 3-((.+-.)2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid (CPP) and analogs; (e)-4-(3-phosphonoprop-2-enyl) piperazine-2-carboxylic acid (CPPenes) and analogs; cis-4-phosphonomethyl-2-piperidinecarboxylic acid (CGS 19755); DL-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid (CGP 40115) enantiomers and analogs; S-.alpha.-amino-5-phosphonomethyl-[1,1'-biphenyl]-3-propanoic acid, E-2-amino-4-methyl-5-phosphono-3-pentenoic acid, E-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester, cis-4-phosphonomethyl-2-piperidinecarboxylic acid, (R)-4-oxo-2-amino-5-phosphono-pentanoic acid, 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid, 4-(phosphonomethyl)-DL-phenylglycine, 4-(3-phosphonopropyl)-2-piperidinecarboxylic acid, 2-(2-phosphonoethyl)-DL-phenylalanine, 3-carboxy-5-(phosphonoethyl)-1,2,3,4-tetrahydroisoquinoline, 3-carboxy-5-phosphono -1,2,3,4-tetrahydroisoquinoline, cis-DL-4-[(1(2)H-tetrazol-5-yl)methyl]2-piperidinecarboxylic acid, cis-4-(3-phosphonoprop-1-enyl)-2-piperidinecarboxylic acid, E-2-amino-4-propyl-5-phosphono-3-pentenoic acid, phosphoric acid-4-(2-carboxy-piperidinyl) ester, and 1-[4(4-chloro-.alpha.,.alpha.-dimethylbenzyl)-2-methoxyphenyl]-1,2,4-tria- zole-3-carboxylic acid amide. Noncompetitive NMDA antagonists include memantines and other amantadine analogs; budipine and analogs; ifenprodil and analogs; antagonists of the glycine binding site kynurenic acid and analogs; 1-hydroxy-3-aminopyrrolidin-2-one (HA-966) and analogs; polyamines such as spermine and spermidine and analogs: inhibitors of the excitatory amino acid synthesis.

When used as an anesthetic, i.e., to substantially eliminate all sensation, the dosage range is broadly from 1 mg/kg to 15 mg/kg, and preferably from 1 to 4.5 mg/kg over a period of about 1 minute delivered I.V. and 6.5 to 13 mg/kg via intramuscular injection.

On the other hand, when ketamine is used as an analgesic, i.e., to reduce or eliminate pain, the dosage range is broadly from 0.01 mg/kg to 1 mg/kg, and preferably from 0.05 mg/kg to 0.7 mg/kg.

The preservatives used in the invention are benzalkonium chloride quaternary ammonium salts. These compounds have the formula:

##STR00001## wherein X is a halide. The phenyl ring may also have a Cl substitution. The R is an alkyl group having from 10 to 22 carbon atoms, preferably 12 to 16 carbon atoms. The X may be bromide or iodide, but is preferably chloride. Most preferably R is a mixture containing C.sub.12 and C.sub.14 alkyl groups, and X is most preferably chloride, otherwise known as benzalkonium chloride.

The amount of the preservative administered ranges from about 0.001% to about 0.2% per unit dose, preferably from about 0.07% to about 0.14% per unit dose.

Other agents may be used in the invention, for example those that can be used for delivery including liposomes, microparticles (including microspheres and microcapsules) and other release devices and forms that provide controlled, prolonged or pulsed, delivery or which enhance passage through the blood brain barrier. Suitable pharmaceutical carriers, known to those skilled in the art, may also be used. These are described in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Co., Easton, Pa., p.1418 (1985), a standard reference text in this field, incorporated herein by reference. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA.

Administration of the NMDA receptor antagonist can be by way of oral, transmucosal (buccal, nasal and rectal), transdermal, intramuscular, or intraocular route, or by parenteral administration. The parenteral routes of administration include, but are not limited to, intravenous, intramuscular, intrathecal, epidural, intracerebroventricular, intradermal/intracutaneous, or subcutaneous injections. Other parenteral routes may include intraarticular (into the joints), intrasynovial (a joint-fluid area), intraspinal, intra-arterial, and intracardiac. Any two or more routes of administration can be combined, such as intravenous and transdermal.

As those skilled in the art recognize, many factors that modify the action of the active substance herein will be taken into account by the treating physician such as the age, body weight, sex, diet and condition of the patient, the time of administration, the rate and route of administration, and so forth. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the experimental data provided herein.

The present invention is intended for use in animals. In a preferred embodiment, the invention is used with mammals. In another embodiment, the invention is directed to use in humans. The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the invention and how to make and use them.

As used herein, the term "antagonist" refers to a compound that renders the active agent unavailable to produce a pharmacological effect. In other words, the antagonist, itself, does not produce a particular pharmacological effect, but rather blocks the ability of an active agent to produce that effect. In a specific embodiment, the antagonist interacts with the same receptor as the active agent and inhibits the interaction of the active agent with the receptor. The term "antagonist" as used herein includes any compound that reduces the flow of cations through an ionotropic receptor such as NMDA, i.e., a channel closer, and which has not been observed to increase the flow of cations through the same receptor.

A "therapeutically effective amount" of a drug is an amount effective to demonstrate a desired activity of the drug. According to the instant invention, in one embodiment a therapeutically effective amount of ketamine is an amount effective to alleviate, i.e., noticeably reduce, pain in a patient. In another embodiment, a therapeutically effective amount is an amount effective to enhance another pain therapy, e.g., a pain medication such as a narcotic. In still another embodiment, it is an amount effective to induce anesthesia.

The term "neurotoxicity" as used herein refers to the level of neuron degeneration or necrosis, e.g., as measured by neuronal vacuolation or behavioral changes after exposure to the NMDA antagonist composition. The NMDA receptor antagonist formulation of the present invention is one in which the neurotoxicity of the composition is reduced or close to none. The term "close to none" means a level of neurotoxicity, if any, that cannot be detected by a particular assay method.

The term "nontoxic" as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established criteria, is susceptible to approval by the FDA for administration to humans. The term "nontoxic" is also used herein to describe the NMDA receptor antagonists, or blockers, that are useful in the practice of the present invention from NMDA receptor antagonists such as MK-801 whose toxicities effectively preclude their therapeutic use.

As used herein, the term "pharmaceutically acceptable" refers to a biologically or pharmacologically compatible for in vivo use, and preferably means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The following Example(s) illustrate the invention, but are not limiting.

EXAMPLE 1

Randomized, Placebo-Controlled, Double Blind Study of the Safety and Efficacy of PMI-100 for the Treatment of Breakthrough Pain in Patients with Chronic Malignant Pain

This example evaluates the safety and efficacy of a ketamine hydrochloride formulation with preservative delivered through a nasal spray. Plasma levels were measured for the bioavailability and for correlating blood levels with analgesic effect.

Methods

The study is a randomized, multi-center, placebo-controlled, double-blind, crossover trial with 20 patients who had chronic malignant pain and a pattern of 2-7 episodes of daily breakthrough pain, despite taking stable doses of analgesic medication. After an initial screening visit (visit 1), patients completed 2 study visits at least 48 hours apart; one visit for treatment with a PMI-100 formulation (visit 2), and a second visit for treatment with placebo (visit 3). The PMI-100 formulation is an aqueous intranasal ketamine formulation containing 10% (w/v) ketamine hydrochloride solution and 0.002% benzalkonium chloride solution. The placebo control is an aqueous solution of 0.002% benzalkonium chloride solution alone.

When pain intensity at the onset of breakthrough pain episodes were greater than or equal to 5 on the Numeric Pain Intensity Scale (NPIS), patients self-administered 1-5 sprays (90 seconds apart, alternating nostrils) of the PMI-100. If the episode was less than 5, the patients were advised to wait for another episode. Treatment duration varied depending on the number of sprays of study medication administered by the patient.

The primary efficacy parameter was the difference between the average of the 9 post-treatment NPIS measurements and the baseline pre-treatment NPIS pain measurement. Secondary efficacy parameters included: NPIS pain measurements at each of 10 time points, the Investigator's opinion of the treatment response (rated as "good," "fair," or "poor"), and the proportion of subjects with at least a 40% reduction of the NPIS measurement from baseline to the end of treatment; where "end of treatment" was defined as the average of the 9 post-baseline NPIS scores. Another parameter of interest was the proportion of subjects who took rescue medication during the breakthrough pain episode.

Safety assessments consisted of monitoring and recording all adverse and serious adverse events, measurement of hematology and blood chemistry parameters, measurement of vital signs, measurement of nasal symptoms, including an assessment of the side effects utilizing a rating scale for dissociative

anesthetics. The primary safety parameter was the results from the Side Effects Rating Scale for Dissociative Anesthetics. The scale was administered immediately after the final NPIS rating was done (approximately 60 minutes after the first administration of study medication) and then again 24 hours after administration of the study drug.

Patients were asked to rate any of the side effects included in the scale that may have occurred since using the study medication. Side effects that were rated included: fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, changes in vision, mood change, generalized discomfort and hallucination. The degree of severity of each of these side effects was rated as: 0=No change; 1=weak; 2=modest; 3=bothersome; 4=very bothersome. Other adverse events were recorded separately. The Investigator recorded on the CRF whether each adverse event was best described as UNRELATED, POSSIBLY RELATED, PROBABLY RELATED, DEFINITELY RELATED or of UNKNOWN association to the study medications.

Hematology [hemoglobin, hematocrit, PT, PTT, red blood cells (RBC), white blood cells (WBC) with differential and platelet count], blood chemistry [sodium, CO.sub.2, potassium, calcium, phosphorous, chloride, glucose, blood urea nitrogen, serum creatinine, serum uric acid, total serum protein, serum albumin, total bilirubin, lactate dehydrogenase (LDH), liver function tests (AST, ALT, alkaline phosphatase)], were measured prior to the treatment and after the treatment at both Visits 2 and 3.

Plasma levels of ketamine and its metabolites were measured at baseline, and at 2 minutes, 30 minutes, and 60 minutes following the last spray of study medication for each patient.

Vital signs (body temperature, systolic blood pressure, diastolic blood pressure, pulse oximetry and heart rate) were measured at Visit 1 (screening), and pre-treatment, during treatment (at 10, 20, 40 and 60 minutes) and post-treatment at Visits 2 and 3.

Nasal symptoms included the incidence of nasal pain, nasal congestion, sinus pain, sinus headaches, nosebleeds, change in smell, change in taste, runny nose, bad odor in nose, dry nose, postnasal drip, excess tearing and headaches.

The severity of break through pain episodes was rated using a Numeric Pain Intensity Scale (NPIS). The NPIS is a commonly used tool for the assessment of pain. The Side Effects Rating Scale for Dissociative Anesthetics provides an assessment of experiences likely to be induced by near-anesthetic doses of drugs such as ketamine. The use of ketamine hydrochloride as an anesthetic agent has resulted in the occurrence of postoperative confusional states known as "emergence reactions" in approximately 12 percent of patients. The psychological manifestations have varied in severity, and in some cases have been accompanied by confusion, excitement, and irrational behavior recalled by a few patients as an unpleasant experience. The duration ordinarily was no more than a few hours; in a few cases, however, recurrences took place up to 24 hours postoperatively. Thus the Side Effects Rating Scale for Dissociative Anesthetics was administered immediately after treatment (approximately 60 minutes after the first dose of study medication) as well as 24 hours after treatment with study medication.

Efficacy.

The primary efficacy analysis consisted of a two-stage crossover analysis of a summary measure of change in NPIS pain measurement. The summary measure of change in NPIS pain measurement was calculated by averaging the 9 post-treatment NPIS pain measurements, and then subtracting the baseline NPIS pain measurement. The tests for a differential carryover effect and period effect were performed using Wilcoxon rank sum statistics with exact critical values. If no carryover or period effects were noted, treatment effect was assessed by comparing within patient differences using the Wilcoxon signed

rank test. If a significant carryover effect was detected, treatment effect was assessed using Visit 2 data only, with the Wilcoxon rank sum test. The Wilcoxon signed rank statistic and the Wilcoxon rank sum tests were obtained using exact critical values.

As a secondary analysis, if there was no evidence of a carry-over effect in the primary analysis, a Friedman's Repeated Measures Analysis of Variance on Ranks test was used to compare the NPIS responses at the 10 time points within each treatment group. If there was a statistically significant carry-over effect ($p<0.10$) in the primary analysis, then the Friedman's test was calculated on Visit 2 data only. Secondary analyses also included the proportion of subjects who exhibited at least a 40% reduction in NPIS from baseline to the end of treatment (where "end of treatment" was defined as the average of the 9 post baseline NPIS scores), with PMI-100 vs placebo. These proportions were compared using the exact version of McNemar's test for matched proportions.

The investigator's opinion of response to therapy under each treatment regimen was summarized as a cross tabulation table. The exact version of the marginal homogeneity test was performed. Another parameter of interest was the proportion of evaluable subjects who chose to use rescue medication during the breakthrough pain episode under the placebo condition, versus the proportion who chose to use it under the active treatment condition. These figures were described by cross tabulations and compared by the exact version of McNemar's test for matched proportions.

Safety.

Cross tabulations of the responses by treatment were presented for the Side Effects Rating Scale for Dissociative Anesthetics evaluated post-evaluation and 24-hours post-evaluation. The exact version of the marginal homogeneity test was performed. The incidence of adverse events by treatment and by visit were displayed for all adverse events, serious adverse events and associated adverse events. For routine laboratory and chemistry parameters and vital signs, continuous outcomes were analyzed using the Wilcoxon Signed Rank test. In addition, summary statistics (sample size, mean, median, standard deviation, and range) were also presented for each treatment. The number and percent of patients experiencing specific nasal complaints under each treatment were tabulated.

Plasma levels of ketamine and its metabolites (norketamine and dehydronorketamine) were measured and listed for each patient at baseline, 2 minutes, 30 minutes, and 60 minutes following the last spray of study medication. 10 ml blood samples were drawn, and replaced with 10 ml saline. The blood samples were drawn into a heparinized tube, which was subsequently gently inverted 10 to 15 times, and centrifuged until cells and plasma were separated. At least 5 ml plasma were transferred into 7 ml storage vial, labeled, and frozen immediately at -20.degree. C.

Results

Treatment of breakthrough pain with PMI-100 demonstrated significant reductions in pain intensity compared to treatment with placebo in this cross-over study. Mean reduction from the baseline NPIS pain score was 2.65 (mean summary measure of change over the 9 post-treatment observation time points) units in the PMI-100 treatment group compared to 0.81 units in the placebo treatment group ($p<0.0001$). Fifteen of 20 (75%) of patients administered the maximum 5 sprays of PMI-100. Statistically significant reductions in pain intensity compared to placebo occurred as early as the 10 minute observation period, or 4 minutes following administration of the 5 spray, and significance continued through the 60 minute observation time point. Nineteen of 20 patients (95%) reported reduction in pain intensity within the 60 minute observation period after treatment with PMI-100, while only 10 of these 20 patients (50%) reported a reduction after treatment with placebo. Nine patients (45%) had an average reduction in NPIS score of 40% or greater following treatment with PMI-100

compared to only one patient (5%) following treatment with placebo(p=0.0078). Zero out of 20 patients requested rescue medication during the 60-minute breakthrough pain episode observation period while 7 of 20 (35%) requested rescue medications after treatment with placebo (p=0.0156).

The investigator's global assessment of the patient's general condition following study medication was "good" for 16 of 20 (80%) patients, irrespective of whether the patient was being treated with PMI-100 or placebo. After PMI-100 treatment, 18 of 20 (90%) patients were assessed as "good", one patient was assessed as "fair" and only one patient was assessed as "poor". Four patients were assessed as "poor" during treatment with placebo.

After treatment with PMI-100, 13 of 20 (65%) patients achieved a minimum NPIS score that was at least 40% lower than the pre-treatment score, compared with only 4 of 20 (20%) in the placebo group. The clinical significance of this effect is further demonstrated by the observation that 14 of 20 (70%) patients treated with PMI-100 achieved a NPIS score of 4 or less, the target used by most pain guidelines, and 11 of 20 (55%) patients attained a minimum NPIS score of 2.2 or less while an equivalent reduction in NPIS score was achieved only in 2 of 20 (10%) patients after treatment with placebo. By contrast, after administering treatment with placebo, 10 of 20 (50%) patients reported no reduction in NPIS score during the 60 minute breakthrough pain episode while only 1 patient reported no relief after treatment with PMI-100.

Equally impressive from a clinical perspective, is the rapidity of pain relief, with 15 of 20 (75%) achieving their minimum NPIS score within 25 minutes, and 8 achieving their minimum NPIS score within 5-10 minutes following treatment with PMI-100. Statistically significant pain relief occurred within 4 minutes of the delivery of the final intranasal spray of PMI-100 (10 minutes from initial spray). See Table A below.

TABLE-US-00001 TABLE A NPIS Score-Change from Baseline over Time-Modified Intent-to-Treat Population Time after Start of Administration of Study Drug (Minutes).sup.a 5 10 15 20 25 30 40 50 60 PMI-100 -1.50 -2.45 -2.79 -2.51 -3.03 -2.98 -3.13 -2.86 -2.47 Placebo -0.56 -0.67 -0.83 -0.83 -0.94 -0.96 -0.79 -0.77 -0.98 P-value.sup.b 0.2114 0.0039 0.0007 0.0010 0.0003 0.0007 0.0001 0.0001 0.0037 .sup.aAdminisrtation of PMI-100 may not have completed until 7.5 minutes after start of dosing .sup.bWilcoxon signed rank test comparing change between treatment groups

A statistically significant between-treatment difference in the mean change of the NPIS score was observed as early as 10 minutes after initiation of treatment and persisted for remainder of the 60 minute observation period. For the 15 (75%) patients administering 5 sprays, statistically significant changes in NPIS score occurred as early as 4 minutes following the final spray. The greatest improvements in the NPIS score occurred in the PMI-100 treated group between 25 and 40 minutes after initiation of treatment. This corresponds with plasma levels of ketamine that were higher at the 30 minute post final spray observation point compared to the 2 minute and 60 minute post final spray observation points. Analyses were repeated for a per-protocol population. Analyses suggested evidence of a period effect (p=0.0350) although subjects who were administered PMI-100 still had an advantage over those administered placebo at both Visit 2 (3.46 units vs. 1.20 units, p=0.0734) and Visit 3 (2.05 units vs. 0.45 units). Results from the GEE analysis suggested that after adjusting for a period effect (p=0.0207), the reduction from baseline was on average 1.93 units greater following treatment with PMI-100 than placebo (p=0.0029).

Based on the NPIS score reported, a rank was assigned to each of the 10 visit time points for each patient. The maximum rank that could be assigned to a time point was 10. However, if a patient reported the same NPIS score at more than one time point, the average rank would be assigned to each of those equivalent time points. The median of the ranks of the 20 patients was then calculated at each time point.

The median rank of the pre-treatment time point (time 0) was 9.5 for patients following PMI-100 treatment and the 25.sup.th-75.sup.th percentile range was 8.3 to 10.0. This would imply that the pain of maximum intensity was felt at time 0. Over time the median dropped and the range of the distribution shifted lower. At 60 minutes the median was 6.8 with a 25.sup.th-75.sup.th percentile range of 3.0 to 8.5. Friedman's test p-value of <0.0001 (0.0007 following treatment with placebo) suggests that there is a difference in the distribution of ranks over the 60 minutes, and the contrast p-value of <0.0001 (0.0386 following treatment with placebo) indicates that there is a difference between time 0 and the average of the post-treatment values.

Following the administration of study medication, the investigator evaluated the patient's general condition as good, fair or poor. Since the investigator's global assessment was "good" following either PMI-100 or placebo treatment for 16 of 20 (80%) patients, this assessment proved not to have discriminatory potential. This group included all 15 patients evaluated at Site 01. Three patients were assessed as "poor" following treatment with placebo and required rescue medication during the breakthrough pain episode. Of the 20 patients in the study, only patient 164 from Site 03, received an assessment of "poor" after treatment with PMI-100. Patients in the per-protocol population were assessed as "good" following treatment with both PMI-100 and placebo.

The number of patients that were able to attain a 40% reduction in NPIS score from the pre-treatment score to the mean of the 9 post-treatment observations was compared between treatment with PMI-100 and treatment with placebo. Nine of 20 (45%) patients attained a mean of the 9 post-treatment observations that represented at least a 40% reduction from their pre-treatment NPIS score following treatment with PMI-100. These were patients 106, 107, 110, 112, 115, and 117 from Site 01 and 162,163 and 165 from Site 03. Patient 110 from Site 01 also attained a 40% reduction following treatment with placebo. This treatment difference in ability to attain a greater than 40% reduction in NPIS score was shown to be statistically significant compared to placebo (p=0.0078) using McNemar's test for paired data.

Use of rescue medication during the 60-minute breakthrough pain evaluation period was compared between patients being treated with PMI-100 and those being treated with placebo. Zero of 20 patients required rescue medication during the breakthrough period when treated with PMI-100, compared to 7 of 20 patients that required rescue medication during the breakthrough period after treatment with placebo (p=0.0156).

Efficacy Conclusions.

The results of the study indicate that intranasal ketamine hydrochloride (PMI-100), administered at doses ranging from 10 mg to 50 mg, provides rapid, meaningful pain relief during intense breakthrough pain episodes that otherwise are poorly managed. Placebo control had no effect in alleviating pain. The onset of statistically significant reductions in pain intensity after treatment with PMI-100 was within 10 minutes of the first spray, and within 4 minutes for patients who administered the full 5 sprays. Furthermore, 75% of patients treated with PMI-100 achieved their minimum NPIS score within 25 minutes of administration. The magnitude of the average decrease in pain intensity compared to placebo was statistically significant over the 60 minute observation period, and a statistically significant number of patients averaged a >40% reduction in their NPIS scores. The time-specific significant reductions in pain intensity after treatment with PMI-100 started at 10 minutes and continued through the 60 minute observation point. The efficacy data presented here is clinically significant. Zero of 20 patients required use of rescue medications in the 60 minutes following administration of PMI-100, representing the potential for lower daily opioid use. Although patients were not required to administer 5 sprays, or 50 mg, of PMI-100 the majority (75%) did, indicating that the therapeutic dose is possibly towards the higher end of the range. Patients who delivered less than 5 sprays did indicate substantial reductions in

pain intensity however, which supports a self-titrating approach might be necessary with this test product.

Safety Evaluation.

Using the Rating Scale for Dissociative Anesthetics, which was a retrospective questionnaire administered to each patient 60 minutes post-study drug administration, possible dissociative-type side effects were evaluated. The questionnaire was administered again 24 hours after study drug administration to evaluate any lingering effects of intranasal ketamine.

Overall there were few dissociative side effects reported, and the majority of effects were mild to moderate in severity and had resolved by the time the questionnaire had been administered 60 minutes after dosing. Nine of 20 (45%) patients reported some type of dissociative effect following treatment with PMI-100 compared to only 1 (5%) patient after treatment with placebo. The most commonly reported effects reported on the questionnaire after treatment with PMI-100 were fatigue (7 patients), dizziness (4 patients), feeling of unreality (4 patients), and changes in vision (2 patients). Of these commonly reported effects, less than 10% of the treatment group indicated that they were "bothersome" or "very bothersome" in nature. Only one patient (5%) indicated a "general feeling of discomfort" after treatment with PMI-100. With the exception of 2 patients with fatigue, and one patient with nausea, there were no side effects reported on the 24 hour post-drug administration dissociative side effects questionnaire. There were no reports of hallucinations following treatment with intranasal PMI-100, nor were any interventions with benzodiazipines required.

The majority of bothersome and very bothersome dissociative effects reported were experienced by three patients, all of whom administered the maximum 5 sprays of PMI-100: 1) Patient 165 experienced very bothersome dizziness and feeling of unreality post-evaluation. The patient also experienced dizziness and headache during placebo administration. This patient also had a fluctuation of blood pressure, with a pre-episode blood pressure of 142/86. Twenty minutes into the breakthrough pain episode, the patient's blood pressure rose to 169/88. At post-evaluation, the patient's blood pressure was 103/53. 2) Patient 117 experienced 7 side effects post-evaluation which included fatigue (bothersome), dizziness (bothersome), feeling of unreality (moderate), change in hearing (moderate), change in vision (mild), mood change (moderate), and generalized discomfort (bothersome). 3) Patient 105 experienced fatigue (bothersome), feeling of unreality (bothersome), and a change in vision (moderate) at post-evaluation. It should be noted that this patient had a medical history significant for blurry vision in the past, so this is possibly not related to the drug.

No patients, following administration of either PMI-100 or placebo, experienced dizziness 24 hours post evaluation. No patients, following administration of either PMI-100 or placebo, experienced headache post-evaluation, or 24 hours post-evaluation. No patients, following administration of either PMI-100 or placebo, experienced a feeling of unreality 24 hours post-evaluation. No patients, following administration of either PMI-100 or placebo, reported changes in hearing 24 hours post-evaluation. No patients, following administration of either PMI-100 or placebo, experienced changes in vision 24 hours post-evaluation. No patients, following administration of either PMI-100 or placebo, reported mood change 24 hours post-evaluation. No patients, following administration of either PMI-100 or placebo, experienced generalized discomfort 24 hours post-valuation.

A pre- and post-treatment nasal symptom assessment was performed as part of the safety assessment of PMI-100 and placebo. The nasal spray, at a concentration of 100 mg/ml, and a dose of 10 to 50 mg (one to 5 sprays), was very well tolerated with few effects noted on the nasal symptom exam. A change in taste that was not present pre-treatment was reported for 3 patients (#162, 163 and 165 from Site 03) following treatment with PMI-100. Nasal congestion, sinus pain, runny nose and post-nasal drip were

also reported nasal symptoms. These symptoms were all present pre-treatment and may or may not have been observed post-treatment.

A total of 10 patients experienced adverse events after treatment with either PMI-100 or placebo. All but 4 treatment-emergent adverse events were considered to be associated treatment emergent adverse events, those events deemed by the investigator as either possibly, probably, or definitely related to the study medication. Six of 20 (30%) patients that received PMI-100 experienced an associated treatment-emergent adverse event categorized under the body system of nervous system disorders. Two of 20 (10%) patients that received placebo reported adverse events that fell into this category.

Two of 20 (10%) patients experienced a moderate elevation in blood pressure within 15 minutes following administration of the full dose (50 mg) of PMI-100. Patient 164 had an initial pre-episode blood pressure of 165/69 prior to treatment with PMI-100. During this breakthrough pain episode, the patient's blood pressure rose to 212/88. Approximately 60-minutes after the first spray of PMI-100 the patient's blood pressure was 191/84. This adverse event fell under the body system "investigations" and had a preferred term of "blood pressure increased." This patient's blood pressure also rose during the breakthrough pain episode that was treated with placebo. The patient had a pre-episode blood pressure of 155/70. At 60-minutes, the patients' blood pressure had risen to 187/85, and then dropped back down to 154/73 at post-evaluation. Patient 165 also experienced an increase in blood pressure during the breakthrough pain episode that was treated with PMI-100. The patient's pre-episode blood pressure was 142/86. At 20-minutes, the patient's blood pressure had risen to 169/88. At post-episode evaluation, the patient's blood pressure had dropped to 103/53. This adverse event fell under the body system of "vascular disorders" and had a preferred term of "hypertension NOS."

Only 4 treatment-emergent adverse events were considered not associated to the study medication, 2 occurred following treatment with placebo (mild laceration, nausea) and 2 following treatment with PMI-100 (pyrexia, nasal congestion). No serious treatment emergent adverse events occurred during the study. One patient (165) from study Site 03 experienced a serious adverse event during the screening phase of the study. Patient 165 experienced intractable vomiting and was hospitalized due to this serious adverse event. This event was considered unrelated to the study medication, since the patient had not received any study medication at the time of the event.

Safety Conclusions.

Intranasal ketamine (PMI-100) was well tolerated with no serious adverse events, deaths, or treatment-related drop-outs on study. The majority of adverse events were mild in severity and transient in nature, with "change in taste" or "taste disturbance" being the most frequently reported effect after treatment with PMI-100. During treatment with either PMI-100 or placebo, safety was assessed through the reporting of specific side effects using the Side Effects Rating Scale for Dissociative Anesthetics, the existence of nasal symptoms assessed during a nasal exam, the monitoring of adverse events and the measurement of vital signs, routine hematology and blood chemistry results.

The results from the retrospective solicitation of possible dissociative side-effects indicated that mild, transient fatigue, dizziness, and a feeling of unreality were the most commonly chosen items from the questionnaire. Both dizziness and feelings of unreality were reported by 4 out of the 20 subjects treated with PMI-100, while fatigue was reported by 9/20 patients after treatment with PMI-100. The majority of dissociative effects following treatment with PMI-100 were experienced by 3 patients. The twenty-four hour post study dissociative side effect questionnaire indicated no clinically significant residual effects after treatment with either PMI-100 or placebo, with 2 reports of fatigue, and one report of nausea. There were no hallucinations reported as a result of treatment from either PMI-100, or placebo, and no interventions with benzodiazipines were required.

Two patients experienced moderate elevations in blood pressure within 15 minutes of treatment with PMI-100, which is consistent with known effects of ketamine. Both episodes resolved spontaneously with no sequelae. Vital signs were monitored throughout the study and there were no clinically significant changes. No abnormal laboratory values of clinical significance were reported that could not be attributed to a previous condition.

The overall safety of treatment with PMI-100 for the treatment of breakthrough pain was shown to be similar to treatment with placebo. Although patients experienced more specific side effects after treatment with PMI-100 than after placebo, these transient side effects were mild and might be considered inconveniences rather than obstacles to ketamine treatment.

Discussion and Overall Conclusions

During this 2 site, 2 phase crossover study, patients used an Numeric Pain Intensity Scale to rate their response to self-administered intranasal ketamine hydrochloride (PMI-100) or placebo for the relief of pain of >5 in intensity in 2 separate breakthrough pain episodes. All of these patients were opioid experienced, with daily, around-the-clockopioid regimens equivalent to at least 60 mg/day morphine for the treatment of chronic pain, and additional, short-acting opioids equivalent to at least 5 mg morphine for breakthrough pain episodes. The primary endpoint of the study was to compare the average reduction in pain intensity during a breakthrough pain episode after treatment with PMI-100 compared to placebo. The results of the study indicate that 1 to 5 sprays (10 to 50 mg) of self-administered intranasal PMI-100 compared to placebo demonstrated a highly statistically significant ($p<0.0001$) reduction in average pain intensity over the 60 minute observation period. The average number of sprays administered was 4.65 for PMI-100, indicating a therapeutic effect towards the higher end of the dose range of 10 to 50 mg. All time points from 10 minutes through 60 minutes showed a statistically significant reduction in pain intensity for PMI-100 compared to placebo. The statistically significant reduction in pain intensity within 10 minutes of the initial spray of PMI-100, and 4 minutes of administration of 5 sprays of PMI-100 is clinically relevant. In addition, patients required significantly more additional rescue medication for breakthrough pain episodes treated with placebo than for episodes treated with PMI-100. Considered to be a clinically relevant reduction in pain intensity from baseline, significantly more patients achieved a 40% or greater overall reduction in pain intensity after treatment with PMI-100 compared to treatment with placebo.

Intranasal administration of PMI-100 for the treatment of breakthrough pain was well-tolerated, with no serious adverse events, deaths, treatment-related drop outs, or clinically significant side effects. The nasal spray was well tolerated with a change in taste being the most frequently reported effect after treatment with PMI-100 at a rate of 3/20 (15%) patients. A review of the literature published regarding the use of intranasal ketamine reveals little about the possibility of unpleasant dissociative side effects at sub-anesthetic dose levels of ketamine. In order to understand fully the potential for dissociative effects following intranasal treatment with PMI-100, a retrospective questionnaire was designed for this study that covered the range of psychotomimetic effects that could potentially occur. As with most solicitation tools, the prevalence of reported effects becomes somewhat inflated when providing a "menu" of items to choose from. The results of the side effect questionnaire indicate that the majority of effects were mild and transient, and few patients experienced troublesome disorientation or feelings of unreality, and no patients experienced hallucination or required intervention with benzodiazipines. Given the overall unpleasantness of an intense episode of breakthrough pain despite the use of around-the-clock opioids, the transient effects of ketamine appear to be of no consequence in light of the pain-relieving qualities experienced after treatment during this study.

In conclusion, this randomized, placebo-controlled, double blind, pilot study in 20 patients has

demonstrated that intranasal ketamine is a highly efficacious treatment for malignant and non-malignant breakthrough pain and shows a large margin of safety in patients on chronic opioid therapy. The profile of this experimental treatment as demonstrated from this study is one of rapid onset, transnasal absorption, possible titrateability, ease of use, and acceptance by patients and for these reasons makes it ideally suited for the treatment of breakthrough pain.

EXAMPLE 2

An Acute Subcutaneous Neurotoxicity Study in Rats with PMI-100

This Example evaluates the neurotoxicity of a formulation of ketamine hydrochloride (referred to hereafter as "PMI-100") in rats following a single subcutaneous injection. PMI-100 is a formulation containing 100 mg ketamine/ml and 0.002% benzalkonium chloride. The findings are based on the level of neuronal vacuolation.

Materials and Methods

This study included 160 rats with 16 male and 16 female rats in each of the following five treatment groups: Group 1 was given sterile water for injection (control); Group 2 was given 4 mg/kg PMI-100; Group 3 was given 15 mg/kg PMI-100; Group 4 was given 60 mg/kg PMI-100; and Group 5 was given 0.5 mg/kg MK-801. Four rats of each sex in each of these five groups were allocated to four study subgroups (Subgroups A, B, C, and D). The rats in Subgroup A were necropsied approximately six hours post-dose. Those in Subgroup B were necropsied approximately 24 hours post-dose. The rats in Subgroup C were necropsied approximately 72 hours post-dose, and those in Subgroup D were necropsied 14 days post-dose. Tabel A illustrates the specific criteria of each group and subgroup. Table B illustrates the details of the subgroups and the stains employed for evaluating the brain sections.

TABLE-US-00002 TABLE A Experimental Study Design - Acute Neurotoxicity Study Approximate Dose Dose No. of Animals Dose Dose Level Conc. Volume Group Male Female Material (mg/kg) (mg/mL) (.mu.L/kg) 1 16 16 Vehicle 0 0 600 2 16 16 PMI-100 4 100 50 3 16 16 PMI-100 15 100 150 4 16 16 PMI-100 60 100 600 5 16 16 MK-801 0.5 5 100

TABLE-US-00003 TABLE B Subgroup Information - Acute Neurotoxicity Study Designation Study Purpose Subgroup A Animals euthanized at ~6 hours post-dose (day 0) primarily for evaluation of neuronal vacuolation (H&E staining) Subgroup B Animals euthanized at ~24 hours post-dose (day 1) primarily for evaluation of neuronal vacuolation (H&E staining) and neuronal necrosis (Fluro-jade/DAPI staining). Subgroup C Animals euthanized at ~72 hours post-dose (day 3) primarily for evaluation of neuronal necrosis (Cupric Silver staining). Subgroup D Functional Observation Battery, ("FOB") and learning/memory evaluations conducted on this Subgroup. Animals euthanized at 14 days post-dose (day 14) primarily for evaluation of neuronal necrosis (Cupric Silver staining).

Histotechnology Procedures.

Prior to necropsy, the rats were anesthetized and then subjected to intracardiac perfusion for optimal fixation. The brains of rats in Subgroups C and D were removed and imbedded in a gelatin matrix (16 brains in each block), frozen, serially sectioned at 40 micrometers. Representative step sections (between 33 and 34 for each rat) were stained with a cupric silver stain according to the method of de Olmos, which is incorporated herein by reference (Fix et al., Toxicol. Pathol. 1996, 24:291-304; Switzer, R. C., New York Acad. Sci. 1993, 679:341-348; Switzer, R. C., Toxicol. Pathol. 2000, 28:70-83). Of the 33-34 sections present for each rat brain, approximately 17 included the posterior cingulate and retrosplenial cortices.

The brains from the rats in Subgroups A and B were completely sliced in a standardized fashion to yield nine coronal sections, with each coronal slice being between 2-3 millimeters in thickness. Of these nine coronal sections, one included the posterior cingulate cortex, while three passed through the retrosplenial cortex. Two sagittal sections of the olfactory bulbs were also prepared. The coronal brain slices were placed anterior face down (the olfactory bulbs medical surface down) within tissue cassettes, processed to paraffin with a Citadel.RTM. tissue processor (Shandon Lipshaw), and embedded in paraffin following standardized procedures. The paraffin blocks were sectioned at a thickness of approximately 5 micrometers using a rotary microtome. All brain sections from the rats in Subgroups A and B were stained with hematoxylin and eosin (H&E). In addition, duplicate sections of brain from the rats in Subgroup B were also stained with Fluoro-Jade B, using DAPI (4', 6-diamidino-2-phenylindole) as a counterstain. The Fluoro-Jade B procedure has been described previously in Schmued, L C and Hopkins, K J., Brain Research 2000, 874:123-130 and in Schmued, L C and Hopkins, K J., Toxicologic Pathology 2000, 28:91-99, which are both incorporated herein by reference.

The cupric silver technique is the most sensitive stain for demonstrating degenerative neurons (i.e., of the three stains used in this study). The H&E stain is the least sensitive (or least specific) stain, with the sensitivity of the Fluoro-Jade B stain lying in between that of the H&E and cupric silver stain. However, the cupric silver stain is frequently also characterized by non-specific staining that may be confused with bone fide neuoronal degeneration. In this study, for example, the lateral hypothalamic area frequently contained well-stained fragmented axons that were present with equal frequency in the control and treated rats. This staining pattern was interpreted as being artifactual in nature and, therefore, was not documented. Similarly, small numbers of axons with a fragmented or "beaded" appearance were frequently found in other regions of the brain. These were not documented unless two or more stained axons were present in relatively close proximity (e.g. within one medium power field). The presence of two or three such stained axons would have received a grade of "minimal" for axonal degeneration. However, in the case of degenerating neurons, even one darkly-stained shrunken neuron would have received a minimal grade for neuronal degeneration. (Note the "neuron degeneration" rather than "neuron necrosis" was used for the cupric silver-stained sections, because it was often not possible to definitively identify a necrotic phenotype with this stain.) Darkly-stained neurons without a necrotic phenotype (e.g. with well preserved nuclear detail) were considered to represent artifactual "dark neurons" and were not documented. Darkly-stained (presumably degenerative) astrocytes within cupric silver-stained sections were also not documented, these cells being present in approximately equal numbers within both control and treated rat brains.

Dark granular staining of scattered glomeruli within the olfactory bulbs of rats is quite common in sections stained with the cupric silver technique and is considered to represent normal background degeneration/remodeling. Although a greater frequency of this staining is evident within treated rats in Subgroup C versus controls, this is not considered to be of biologic significance based on past experience with this stain and this particular staining pattern. Because numerous other studies that have been evaluated have shown mild to moderate degrees of olfactory glomerular degeneration within 100% of control animals, the inter-group differences in this particular study are thought to be the result of two factors: (1) that the control and treated rat brains were embedded in different blocks (i.e., with all 16 control group brains in Subgroups C and D having been blocked, together); and (2) the fact that the degree of this staining varies considerably from section to section.

Minimal degrees of axonal degeneration within cupric silver-stained sections (i.e., usually two or three axons within one intermediate power field) or of neuron degeneration (usually one neuron within one intermediate power field) can be overlooked as representing background change. Therefore, only neuron degeneration graded as being mild or greater in degree within cupric silver-stained sections was considered to be of biologic significance. Such degrees of degeneration were present only in the MK-

801-treated rats.

Microscopic Evaluations.

All slides were examined in "blinded" fashion (i.e., without knowledge of treatment group assignment). The labels present on the microscope slides for Subgroups A and B included the treatment group designation and were, therefore, covered with opaque tape and the animal identifications replaced with letter codes. No labels were present on the cupric silver-stained slides, with only a key being present inside the slide box cover to indicate the animal number for each of the sixteen sections present on each slide. Microscopic findings were hand-recorded by the pathologist onto individual animal work sheets, with one sheet/animal being present for each set of H&E, Fluoro-Jade B, and cupric silver-stained slides. Diagnoses were either hand-written or numbers were used to indicate diagnoses present within a standard list (list included with raw data). All observations were also given one of five grades of severity (minimal, mild, moderate, marked, or severe). Distribution patterns of focal, multifocal, or diffuse were also assigned to any microscopic observations.

After removing the tape to "unblind" the animal numbers and group assignments, the hand-recorded data were entered into a PC-based computer program (GLPATH available from Great Laboratory Programs.RTM.). The computer protocol for this study was set up to include only 31 representative neuroanatomic regions, these having been selected based both on the potential for lesions to develop in these regions and to indicate the levels of brain that were examined. However, all areas/structures within every section were examined, not just the posterior cingulate and retrosplenial cortices.

All 33-34 cupric silver-stained sections per rat (Subgroups C and D) were also examined microscopically.

Results and Discussion

The microscopic findings for this study are discussed by subgroup.

Subgroup A.

The rats in Subgroup A had been euthanized approximately six hours post-injection. Only H&E-stained brain sections were examined from these rats, primarily to look for evidence of neuron cytoplasmic vacuolation (especially within the posterior cingulate and retrosplenial cortices) typical of that seen following treatment with NMDA receptor antagonists such as MK-801 (Fix et al., Toxicol. Pathol. 1996, 24:291-304; Fix et al., Experimental Neurology 1993, 123:204-215). This typical pattern of neuron vacuolation within the retrosplenial cortex, primarily involving neurons within Layers 2 and 3 of the cortex, was limited to the MK-801-treated rats in this study and was most prominent in the female rats. Only one male rat treated with MK-801 had such vacuolation, and this vacuolation was only minimal in degree. While this same male rat (#4876) also had a minimal degree of neuron necrosis within the retrosplenial cortex, it is not certain that this neuron necrosis was the result of the MK-801.

In contrast to the male rats, all four of the Subgroup A female rats treated with MK-801 had mild to moderate degrees of neuronal cytoplasmic vacuolation within the retrosplenial cortex. In addition, two MK-801-treated female rats had minimal to mild degrees of vacuolation within the piriform cortex. While none of the PMI-100-treated rats had evidence of neuronal cytoplasmic vacuolation within any brain section, all four of the high dose group (60 mg/kg) PMI-100-treated rats had minimal to mild degrees of vacuolation within the molecular layer (Layer 1) of the retrosplenial cortex. This vacuolation may indicate the presence of swollen apical dendrites (i.e., from neurons present deeper within the retrosplenial cortex) or swollen axonal terminals belonging to neurons projecting to this region.

However, there was no evidence at later stages of any associated neuron degeneration (see discussion for Subgroups B-D, below). Also, a similar pattern of molecular layer vacuolation was not present within any of the rats injected with MK-801.

In all of the Subgroups, there were minimal degrees of axonal degeneration within the trapezoid body of the brainstem. However, this represents a common background lesion in rats and was found in equal degrees in Control group rats and was not treatment-related.

Subgroup B.

The rats in Subgroup B had been euthanized approximately 24 hours after receiving their single injections. Both H&E and Fluoro-Jade B-stained brain sections were examined from these rats, primarily to detect any residual vacuolation and/or early evidence of neuronal necrosis within the posterior cingulate and retrosplenial cortices. In Subgroup B, one male and several female MK-801-treated rats had minimal to mild degrees of neuron necrosis within the piriform cortex that were detected primarily within the Fluoro-Jade B-stained sections. None of the male rats in Subgroup B (i.e., even those treated with MK-801) had evidence of treatment-related neuron degeneration or necrosis. However, three of the four female rats treated with MK-801had minimal to mild degrees of neuron necrosis within the retrosplenial cortex. The fourth female rat treated with MK-801 was classified as having minimal "neuron, degeneration" (rather than necrosis) within its retrosplenial cortex, because it was not certain whether the microscopic changes represented basophilic neuron artifact or neuron necrosis (e.g. see Garman, R. H., Toxicol. Pathol.1990, 18:149-153.). No rats in Subgroup B that had been injected with PMI-100 had any microscopic evidence of neuron necrosis within any section of brain.

One male control group rat in Subgroup B had evidence of unilateral optic tract degeneration that involved the optic nerve, optic tract, and superior colliculus. This is a common sporadic lesion of rats that is usually unilateral but occasionally bilateral in distribution (Shibuya et al. J Vet Med Sci 1993, 55:905-912.). This lesion was also detected in rats from Subgroups C and D and is not treatment related in this study. As in Subgroup A, numerous rats in Subgroup B had evidence of minimal to mild axonal degeneration within the trapezoid body, but this was also not a treatment-related finding in this study.

Subgroup C.

The rats in Subgroup C had been euthanized approximately 72 hours after receiving their injections, with the brains from these rats having been step-sectioned and stained by the cupric silver technique to detect the presence of neuronal degeneration within the posterior cingulate and retrosplenial cortices, as well as elsewhere within the brain. There were between 33 and 34 sections from each brain.

One MK-801-treated male rat had mild neuron degeneration within the frontal cortex. Two male MK-801-treated rats had mild to moderate degrees of neuron degeneration within the retrosplenial cortex.

Mild to marked degrees of neuron degeneration within female rats were also limited to the rats in the MK-801-treatment group, with no PMI-100-treated rats having similar evidence of neuron degeneration. In the female rats treated with MK-801, such neuron degeneration was present in the piriform cortex and retrosplenial cortex. Two female rats treated with MK-801 also had evidence of mild terminal degeneration within the stratum lacunosum moleculare of the hippocampus. Such terminal degeneration within the hippocampus was not seen in PMI110-treated rats.

One control group male rat in Subgroup C had marked unilateral axonal degeneration within the optic nerve and optic tract indicative of unilateral optic tract degeneration. A similar case of spontaneous optic

tract degeneration was present in one female rat in Group 2 (4 mg/kg PMI-100).

Subgroup D.

The rats in Subgroup D had been euthanized 14 days after receiving their injections, with the brains from these rats being step-sectioned and stained by the cupric silver technique to detect the presence later stages of neuronal necrosis within the posterior cingulate and retrosplenial cortices (as well as elsewhere within the brain). As in Subgroup C, the female rats treated with MK-801 were most prominently affected. (Note that, as with Subgroup C, olfactory bulb glomerular degeneration and minimal degrees of neuron degeneration are not considered to be of any biologic significance.) Mild neuron degeneration was found within the retrosplenial cortex of one MK-801-treated male rat. Neuron degeneration graded as being either "mild" or "moderate" was found in the retrosplenial cortex of all four of the MK-801-treated female rats in Subgroup D. However, as in the other subgroups on this study, no such degeneration was found within any of the brain sections from rats treated with the PMI-100. All four of the MK-801-treated female rats in Subgroup D also had mild synaptic terminal degeneration within the stratum lacunosum moleculare of the hippocampus. However, such degeneration was not found within any brain sections from PMI-100-treated rats.

The brain sections from one male rat in Group 2 (4 mg/kg PMI-100) were characterized by spontaneous optic tract degeneration, a condition already discussed as representing a spontaneous "background lesion."

Conclusions

Blinded microscopic evaluations were performed on brain sections from rats given one subcutaneous injection of either sterile water, MK-801 or the PMI-100 formulation of ketamine hydrochloride. Sections of the brains were examined from 4 female and 4 male rats at each of 6 hours, 24 hours, 72 hours, and 14 days post-injection, with these sections having been stained with either H&E, Fluoro-Jade B, or the cupric silver technique. Neuron vacuolation and degeneration within the retrosplenial cortex of the type typically seen with NMDA receptor antagonists was limited to the rats injected with MK-801 and was most prominent in the female rats. Although these alterations were not present in the rats injected with any of the three dosages of PMI-100 used in this study (viz. 4, 15, or 60 mg/kg), the female rats in the high dose PMI-100 group did have minimal to mild degrees of vacuolation within the molecular layer (Layer 1) of the retrosplenial cortex at 6 hours (within the H&E-stained sections). However, no evidence of neuron degeneration was seen in the females from this dose group at later time points (within sections stained either with H&E, Fluoro-Jade B, or the cupric silver technique). It is likely that the molecular layer vacuolation may represent transient swelling within dendritic or axonal terminals.

This study had no-observable-effect level for the PMI-100 formulation of ketamine hydrochloride in this particular study of 60 mg/kg for the male rats and 15 mg/kg for the female rats. The ketamine hydrochloride formulation containing benzalkonium chloride also did not produce any permanent degenerative alterations.

EXAMPLE 3

A 28-Day Subcutaneous Neurotoxicity Study in Rats in PMI-100

The objective of this study was to evaluate the potential neurotoxicity of the test article in the rat following multiple subcutaneous injections of the PMI-100 formulation containing 10 mg/kg (10% w/v) ketamine hydrochloride and 0.002% benzalkonium chloride solution. The formulation was given once

daily over a 28-day period.

Methods

192 rats were distributed across five treatment groups as indicated in Table A. Summary information, including dosing information and the stains employed for evaluating the brain sections, are presented in Text Tables A and B, below.

TABLE-US-00004 TABLE A Experimental Study Design - Acute Neurotoxicity Study Approximate Dose Dose No. of Animals Dose Dose Level Conc. Volume Group Male Female Material (mg/kg) (mg/mL) (.mu.L/kg) 1 20 20 Vehicle 0 0 600 2 20 20 PMI-100 4 100 40 3 20 20 PMI-100 15 100 150 4 20 20 PMI-l00 60 100 600 5 16 16 MK-801 0.3-0.5 3-5 100

TABLE-US-00005 TABLE B Subgroup Information - Acute Neurotoxicity Study Subgroup Designation Study Purpose Subgroup A Animals euthanized at ~6 hours post-dose (day 27) primarily for evaluation of neuronal vacuolation (H&E staining). Subgroup B Animals euthanized at ~24 hours post-dose (day 28) primarily for evaluation of neuronal vacuolation (H&E staining) and neuronal necrosis (Fluro-Jade/DAPI staining). Subgroup C Animals euthanized at ~72 hours post-dose (day 30) primarily for evaluation of neuronal necrosis (Cupric Silver staining). Subgroup D Functional Observation Battery ("FOB") and learning/memory evaluations conducted on this Subgroup. Animals euthanized at 14 days post-dose (day 41) primarily for evaluation of neuronal necrosis (Cupric Silver staining).

Histotechnology Procedures.

Prior to necropsy, the rats had been anesthetized and then subjected to intracardiac perfusion for optimal fixation. The heads from the rats in Subgroups C and D had been sent to NeuroScience Associates in Knoxville, Tenn. where the brains had been removed and multiply imbedded in a gelatin matrix (with 16 brains in each block), frozen, serially sectioned at approximately 40 micrometers (through the cerebral hemispheres but not into the cerebellum), and representative step sections (between 33 and 34 for each rat) stained with the amino cupric silver stain according to the method of de Olmos et al. (1994; Fix, 1996; Switzer, 1993, 2000).

Of the 33-34 sections present for each rat brain, approximately 17 included the posterior cingulate and retrosplenial cortices.

The brains from the rats in Subgroups A and B were sent to Consultants In Veterinary Pathology, Inc. where the brains were completely sliced in a standardized fashion to yield nine coronal sections, with each coronal slice being between two and three millimeters in thickness. Of these nine coronal sections, one included the posterior cingulate cortex, while three passed through the retrosplenial cortex. Two sagittal sections of the olfactory bulbs were also prepared. The coronal brain slices were placed anterior face down (the olfactory bulbs medial surface down) within tissue cassettes, processed to paraffin with a Citadel.RTM. tissue processor (Shandon Lipshaw), and embedded in paraffin following standardized procedures. The paraffin blocks were sectioned at a thickness of approximately 5 micrometers using a rotary microtome. All brain sections from the rats in Subgroups A and B were stained with hematoxylin and eosin (H&E). In addition, duplicate sections of the brains from rats in Subgroup B were also stained with Fluoro-Jade B, using DAPI (4', 6-Diamidino-2-Phenylindole) as a counterstain. The Fluoro-Jade B procedure that was used is that reported by Schmued et al (2000). (Schmued, L. C., Hopkins, K J (2000) Brain Res. 874:123-130. Fluoro-Jade B: a high affinity fluorescent markers for the localization of neuronal degeneration.; Schmued, L. C., Hopkins, K. J. (2000) Toxicol. Pathol. 28: 91-99. Fluoro-Jade: Novel fluorochromes for detecting toxicant-induced neuronal degeneration.

Microscopic Evaluations.

All slides were examined in "blinded" fashion. Once "unblinded" the animal identifications were entered into a PC-based computer program (GLPATH; Great Laboratory ProgramS). The computer protocol for this study was set up to include between 25 (for the cupric silver-stained sections) and 31 (for the H&E and Fluoro-Jade B-stained sections) representative neuroanatomic regions, these having been selected based both on the potential for lesions to develop in these regions and to indicate the levels of brain that were examined. All 30-34 cupric silver-stained sections/rat were also examined microscopically. For the Subgroup B rats, slightly different diagnoses were used for findings made on H&E-stained sections and on those stained with Fluoro-Jade B. For example the term "neuron necrosis" indicates the presence of "red dead neurons" as seen with H&E. However, neuron necrosis within a Fluoro-Jade B-stained section would have received a diagnosis of "Fluoro-Jade Staining."

Results

Subgroup A.

The rats in Subgroup A had been euthanized approximately six hours after their final subcutaneous injections. Only H&E-stained brain sections were examined for evidence of neuron cytoplasmic vacuolation typical of that seen following treatment with NMDA receptor antagonists such as MK-801 (Fix et al., 1993, 1996) (Fix, A. S., Horn, J. W., Lightman, K. A., Johnson, C. A., Long, G. G., Storts, R. W., Farber, N. Wozniak, O. F., Olneg, J. W. (1993), Exp. Neruol. 123: 204-215. Neuronal vacuolization and necrosis induced y the non-competitive N-methyl-D-aspartate (NMDA antagonist MK(+)801, (dizocilpine maleate), a light and electron microscopic evaluation of the rat retrosplineal cortex.; Fix, A. S., Ross, J. F, Stitzer, S. R. Switzer, R. C. (1996) Toxicol Pathol. 24: 291-304. Integrated evaluation of the central nervous system lesions: stains for neurons, astrocytes, and microglia reveal the spatial an temporal features of MK-801 induced neuronal necrosis in the rat cerebral cortex.)

This pattern of neuron vacuolation (which typically involves neurons within Layers II and III of the retrosplenial cortex) was not found within any of the rats in this phase of the study. For the females in Subgroup B, one rat in each of Groups 1 and 2 plus two rats in Group 5 (i.e. MK-801-treated) had minimal neuron necrosis considered to be within background frequency and to be of no biologic significance.

Subgroup B.

The rats in Subgroup B had been euthanized approximately 24 hours after the final injection. Both H&E and Fluoro-Jade B-stained brain sections were examined from these rats to detect any residual vacuolation and/or early evidence of neuronal necrosis within the posterior cingulate and retrosplenial cortices. In the male rats, minimal Fluoro-Jade staining was present within the piriform cortex of one rat and in the tenia tecta of another rat. However, such minimal Fluoro-Jade staining is within the expected background frequency.

In the female rats, both minimal to mild neuron necrosis (on H&E) and minimal to mild Fluoro-Jade staining were present within the retrosplenial cortex of either two or three rats in the MK-801-treated group (Group 5). However, no such alterations were seen in rats injected with PMI-100.

Subgroup C.

The rats in Subgroup C had been euthanized approximately 72 hours after receiving their final

injections. The brains from these rats had been step-sectioned and stained by the amino cupric silver technique to detect the presence of neuronal degeneration within the posterior cingulated and retrosplenial cortices, as well as elsewhere within the brain.

Mild to moderate degrees of neuron degeneration were limited, in Subgroup C, to rats injected with MK-801 and were found most frequently within the retrosplenial cortex. The degree of MK-801-associated neuron degeneration was greatest in the female rats. Mild neuron degeneration was also found within the piriform cortex of two MK-801-treated female rats, as was synaptic terminal degeneration within the stratum lacunosum moleculare of the hippocampus. This latter pattern of degeneration was seen in three of four Subgroup C female rats present in treatment Group 5.

Subgroup D.

The rats in Subgroup D had been euthanized 14 days after receiving their final injections, with the brains from these rats being step-sectioned and stained by the cupric silver technique to detect the presence later stages of neuronal necrosis within the posterior cingulate and retrosplenial cortices. No male rats in Subgroup D had any treatment-related histologic alterations, although there were sporadic findings of minimal degrees of neuron degeneration (i.e. only one or two neurons) in a variety of locations but without any evidence of a dose effect. In the female rats in Subgroup D, treatment-related lesions were confined to the retrosplenial cortex of MK-801-treated rats. All four of the female rats treated with MK-801 had mild to moderate degrees of axon degeneration within the retrosplenial cortex. While two females in Group 2 had foci of minimal axon degeneration within the retrosplenial cortex, this alteration was confined to one section level, only, and probably represented artifact. For the MK-801-treated females, on the other hand, the axonal staining and fragmentation was present within multiple sections throughout much of the retrosplenial cortex.

The fact that female rats in Subgroup C that were treated with MK-801 had neuronal degeneration within the retrosplenial cortex but that MK-801-treated females in Subgroup D only had axonal degeneration in this region suggests that the somas of the necrotic neurons had disappeared over the intervening 11 day period.

Discussion

In conclusion, there is no evidence that treatment of rats with PMI-100 formulations of ketamine hydrochloride and benzalkonium chloride, under the conditions of this subacute study, resulted in any neuropathologic alterations. The only treatment-related lesions were in the rats treated with MK-801, with these being the classical late-stage lesions of neuron and axon degeneration within the retrosplenial cortex. Retrosplenial cortex neurons with vacuolated cytoplasm were not found within this subacute phase of the study. Neither was there any evidence of the pattern of minimal to mild vacuolation noted in Layer I of the Group 4 females necropsied six hours after receiving a single subcutaneous dose of PMI-100 (in the previously performed acute study). Finally, no inter-group differences in overall cellularity of the retrosplenial cortices were noted.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated by reference herein in their entireties for all purposes.

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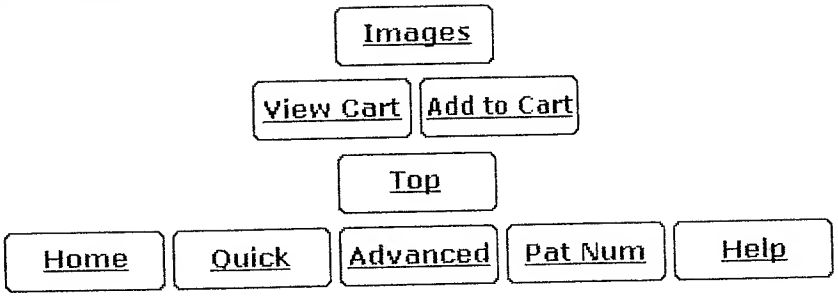
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US005508034A

United States Patent [19]

Bernstein

[11] **Patent Number: 5,508,034**

[45] **Date of Patent: Apr. 16, 1996**

[54] **METHOD AND COMPOSITION FOR TREATING AND PREVENTING DRY SKIN DISORDERS**

[75] Inventor: **Joel E. Bernstein**, Deerfield, Ill.

[73] Assignee: **GenDerm Corporation**, Lincolnshire, Ill.

[21] Appl. No.: **326,034**

[22] Filed: **Oct. 19, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 109,148, Aug. 19, 1993, abandoned, which is a continuation of Ser. No. 994,183, Dec. 21, 1992, abandoned, which is a continuation of Ser. No. 751,610, Aug. 21, 1991, abandoned, which is a continuation of Ser. No. 542,632, Jun. 22, 1990, abandoned, which is a continuation of Ser. No. 231,848, Aug. 12, 1988, abandoned.

[51] **Int. Cl.**[6] **A61K 7/00**

[52] **U.S. Cl.** **424/401**; 514/78; 514/847

[58] **Field of Search** 426/401, 450; 514/77, 78, 841

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Primary Examiner—Gollamudi S. Kishore

[57] **ABSTRACT**

A method and composition for treating and preventing dry skin includes a lipid concentrate blended from a combination of the three naturally-occurring lipid groups found in the stratum corneum. The concentrate may be applied topically as prepared, or may be blended with a therapeutically acceptable vehicle suitable for topical application.

17 Claims, No Drawings

METHOD AND COMPOSITION FOR TREATING AND PREVENTING DRY SKIN DISORDERS

This is a continuation-in-part of application Ser. No. 08/109,148 filed on Aug. 19, 1993; now abandoned, which is a continuation of U.S. Ser. No. 07/994,183, filed Dec. 21, 1992, now abandoned; which is a continuation of U.S. Ser. No. 07/751,610, filed Aug. 21, 1992, now abandoned; which is a continuation of U.S. Ser. No. 07/542,632, filed Jun. 22, 1990, now abandoned; which is a continuation of U.S. Ser. No, 07/231,848, filed Aug. 12, 1988, now abandoned.

This invention relates generally to dermatological preparations and, more particularly, to methods and compositions for treating and preventing dry skin.

BACKGROUND OF THE INVENTION

Dry skin, also known as xerosis or asteatosis, affects millions of Americans each year. Attempts to treat or prevent dry skin have led to the development of a large assortment of skin creams and lotions. All of these creams and lotions have been developed from either the point of view that applying an occlusive lipid such as petrolatum or mineral oil can retard moisture loss from the skin, or that the incorporation of water-soluble materials, such as free amino acids, organic acids, inorganic ions or urea, into the cream, ointment, gel or lotion can trap or retain water in the skin.

It has been demonstrated over the last few years that the stratum corneum of the skin contains certain lipids which may form complicated layers within the stratum corneum thus forming a "water barrier" which prevents water loss from the skin. It has been discovered that formulations may be prepared composed of components of the skin's natural water barrier forming lipid complex and that when these formulations are used by themselves or when they are incorporated into creams, ointments, gels and lotions, the resulting products provide unsurpassed protection against and treatment for dry skin conditions.

In preparing the formulations disclosed herein, combinations of components from three separate classes of lipids occurring naturally in the stratum corneum can be utilized: (1) fatty acids, in either the free acid form or as triglycerides; (2) sterols and sterol esters; and (3) phospholipids and glycolipids.

SUMMARY OF THE INVENTION

The present invention provides an improved method and composition for prophylaxis for or treatment of dry skin, consisting of preparing a formulation composed of representative lipids from the three classes of lipids naturally found in the stratum corneum. Such a formulation may be applied directly or may be incorporated into a cream, ointment, gel or lotion and the resulting product applied in order to prevent or treat dryness of the skin.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

While other lipids may be utilized, the following members of the three classes of stratum corneum lipids combined under this invention have been successfully utilized:

1. Fatty acids: arachidonic, linoleic, linolenic, palmitic, stearic, oleic and docosanoic, all of which may be present in the inventive composition in either the free acid form or as triglycerides;

2. Sterols: cholesterol, which may be present in the inventive composition as either the sterol or as an ester, such as cholesterol sulfate; and
3. Phospholipids and glycolipids: ceramides, cephalin, and lecithin.

It is to be understood that the invention also encompasses the use of other lipids within these three classes and which occur naturally in the stratum corneum, and further encompasses the use of the naturally occurring fatty acids in either their free acid form or as triglycerides, and the naturally occurring sterols in either the sterol form or as esters. The proportions of the three classes vary in selected lipid concentrate formulations but generally fall within the following ranges:

Fatty acids: 25 to 75%
Sterols and sterol esters: 10 to 40%
Phospholipids and glycolipids: 5 to 40%

The resulting lipid concentrate formulation may then be added to cream, ointment, gel or lotion vehicles in weight/weight concentrations ranging from about 1% to about 50%. The following examples further illustrate the invention:

EXAMPLE 1

A therapeutic skin formula to treat and prevent dry skin was formulated by adding 15 gm of a lipid concentrate composed of 30% W/W cholesterol (obtained under the trade designation Loralan-CH from the Lanaetex Products, Inc., Elizabeth, N.J.), 20% W/W lecithin (obtained from American Lecithin Company, Inc., Atlanta, Ga.), and 50% W/W of a mixture of linoleic acid, linolenic acid and arachidonic acid (obtained under the trade designation of EFA complex from Phillip Rockley, Ltd., New York, N.Y.) to a lotion base as follows:

Isopropyl Myristate	5.0%	7.5 gm
Cetyl Alcohol	2.0%	3.0 gm
Glyceryl Stearate and PEG-100 Stearate (Arlacel 165)	5.0%	7.5 gm
Benzyl Alcohol	1.0%	1.5 gm
Lipid Concentrate	10.0%	15.0 gm
70% Sorbitol solution	25.0%	37.5 gm
Distilled Water	52.0%	78.0 gm
TOTAL	100.0%	150.0 gm

This formulation was applied to the dry skin of a 44 year old male and produced noticeably softer more supple skin after only one application.

EXAMPLE 2

A therapeutic moisturizing formulation was prepared consisting of a lipid concentrate containing 10 ml of linoleic acid (obtained from Emery Industries, Cincinnati, Ohio), 10 ml linolenic acid (obtained from Fluka Chemical Corporation, Ronkonkoma, N.Y.), 10 gm of a mixture of lecithin, cephalin and lipositol (obtained under the trade designation of Asolectin from Fluka Chemical Corporation, Ronkonkoma, N.Y.), and 10 gm of cholesterol (obtained under the trade designation of Loralan-CH from the Lanaetex Products, Inc., Elizabeth, N.J.). The resulting mixture was blended to make a cream composed as follows:

Isopropyl Myristate	5.0%	7.5 gm
Cetyl Alcohol	3.0%	4.5 gm
Glyceryl Stearate and	5.0%	7.5 gm

-continued

PEG-100 Stearate (Arlacel 165)		
Benzyl Alcohol	1.0%	1.5 gm
Lipid Concentrate	5.0%	7.5 gm
70% Sorbitol solution	25.0%	37.5 gm
Distilled Water	56.0%	84.0 gm
TOTAL	100.0%	150.0 gm

This formulation was applied to the dry skin on the lower legs of a 43 year old woman. Within 24 hours of twice daily application the treated skin was noticeably softer, more moist and supple.

Tests were also performed to assess the efficacy of the present invention in preventing water loss. Baseline measurements of 15 healthy adult test subjects were performed to determine the barrier-forming properties of different formulations of the present invention, and to compare these properties with those of two commercially-available skin creams, Eucerin*, manufactured by Beiersdorf, Inc., Norwalk, Conn., and Moisturel*, manufactured by Westwood Pharmaceuticals, Inc., Buffalo, N.Y. A Servo Med Evaporimeter was used to measure rate of water loss from a 4.9 cm^2 patch of unprotected skin. Thereafter, formulations of the present invention were applied to the test subjects at separate 4.9 cm^2 test sites, as were applications of Eucerin* and Moisturel* skin creams. Each application consisted of 25 microliters of each formulation.

Lipid Concentrate I consisted of 30% w/w of cholesterol, 20% w/w of lecithin and ceramides, and 50% w/w of the linoleic, linolenic and arachidonic acid mix. Lipid Concentrate II consisted of 15% w/w of cholesterol, 10% w/w lecithin and ceramides, and 75% w/w of the linoleic, linolenic and arachidonic acid mix.

The formulations tested were prepared as follows:

FORMULA I

	Percent by weight
Isopropyl Myristate	5.0
Cetyl Alcohol	3.0
Arlacel 165	5.0
Benzyl Alcohol	1.0
Lipid Concentrate II	10.0
70% Sorbitol Solution	25.0
Distilled Water	51.0
TOTAL	100.0

FORMULA 2

	Percent by weight
Isopropyl Myristate	5.0
Cetyl Alcohol	3.0
Arlacel 165	5.0
Benzyl Alcohol	1.0
Lipid Concentrate II	5.0
70% Sorbitol Solution	25.0
Distilled Water	56.0
TOTAL	100.0

FORMULA 3

	Percent by weight
Isopropyl Myristate	5.0
Cetyl Alcohol	3.0
Arlacel 165	5.0
Benzyl Alcohol	1.0
Lipid Concentrate II	10.0
Vitamin E	1.0
70% Sorbitol Solution	25.0
Distilled Water	500
TOTAL	100.0

Water loss measurements showed that all five formulations tested reduced water loss as compared to the untreated site, with the formulations of the present invention establishing a stronger barrier to water loss than the commercially available preparations. The test results were as follows:

	% change in evaporative water loss
Formula 1	3.4
Formula 2	3.5
Formula 3	3.6
Eucerin ®	3.7
Moisturel ®	3.9
Untreated Site	4.5

While the foregoing has presented specific embodiments of the present invention, it is to be understood that these embodiments have been presented by way of example only. It is expected that others will perceive variations which, while varying from the foregoing, do not depart from the spirit and scope of the invention as herein described and claimed. For example, the invention encompasses lipids within the three classes and naturally occurring within the stratum corneum other than those used in the particular Examples herein, and further encompasses the use of the naturally occurring fatty acids in either their free acid form or as triglycerides, and the use of the naturally occurring sterols in either the sterol form or as esters. None of the foregoing is attempted to in any manner limit the scope of the present invention.

What is claimed is:

1. A method of preventing or treating dry skin for one in need thereof, said method comprising applying topically to said skin a composition comprising a concentrate of naturally occurring stratum corneum lipids, said concentrate comprising:

(a) a mixture of naturally occurring stratum corneum free fatty acids or triglyceride forms of said fatty acid mixtures in a proportion of about 25% to about 75% by weight of concentrate;

(b) naturally occurring stratum corneum cholesterol or esters of said cholesterol in a proportion of about 10% to about 40% by weight of concentrate; and

(c) One or more naturally occurring stratum corneum lipids selected from the group consisting of ceramide, lecithin and cephalin in a proportion of about 5% to about 40% by weight of concentrate.

2. The method of claim **1** wherein said fatty acids are selected from the group consisting of arachidonic acid, linoleic acid, linolenic acid, palmitic acid, stearic acid, oleic acid, and docosanoic acid.

3. The method of claim **1** wherein said cholesterol is cholesterol sulfate.

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(12) **United States Patent**
Bernstein

(10) **Patent No.: US 6,740,330 B1**
(45) **Date of Patent: May 25, 2004**

(54) **METHOD OF TREATING ACNE VULGARIS AND COMPOSITION**

(75) Inventor: **Joel E. Bernstein**, Deerfield, IL (US)

(73) Assignee: **Sirius Laboratories, Inc.**, Vernon Hills, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/847,151**

(22) Filed: **May 2, 2001**

(51) **Int. Cl.**[7] **A61K 6/00**; A61K 7/00; A01N 25/34

(52) **U.S. Cl.** **424/402**; 424/401

(58) **Field of Search** 424/402, 401

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Primary Examiner—Thurman K. Page
Assistant Examiner—S. Howard
(74) *Attorney, Agent, or Firm*—Jones Day

(57) **ABSTRACT**

An article for use in the treatment of acne vulgaris comprises a cloth pledgette impregnated with a composition comprising benzoyl peroxide and an amount of acetone sufficient to solubilize the benzoyl peroxide. In a preferred embodiment, the article is packaged in an individual pouch. A method of manufacturing the article is disclosed.

28 Claims, No Drawings

METHOD OF TREATING ACNE VULGARIS AND COMPOSITION

BACKGROUND OF THE INVENTION

Acne vulgaris is an inflammatory disease of the sebaceous glands characterized by an eruption of the skin, often pustular in nature but not suppurative. Acne is a common affliction of the adolescent and affects a small but significant percentage of the adult population. Acne involvement results in unsightly lesions, particularly on the face, and in some cases results in severe scarring.

There are a variety of methods for treating acne vulgaris including administering various agents either orally or topically to the skin. Nevertheless, acne vulgaris is seldom cured and only can be controlled with difficulty.

One of the most common agents utilized to topically treat acne is benzoyl peroxide. Benzoyl peroxide is contained in a variety of over-the-counter and prescription acne products which take the form of lotions, creams or gels. The exact mode of action of benzoyl peroxide is unknown, but the best evidence suggests an antibacterial effect against an organism Propionibacterium acnes.

Tubes and bottles of acne medicines are the most common ways of packing such topical agents. However, tubes and bottles are inconvenient for patients to carry with themselves to school, camp, office, etc. Consequently, over the last decade a new method of delivering anti-acne agents has evolved based on incorporating active anti-acne ingredients into small cloth towelettes called pledgettes. These pledgettes can then be packaged in a sealed pouch that can be conveniently opened at the time of use. Additionally, since only one dose is opened at a time, several patients can "share" a box of such pledgettes without exposure to one another's germs, dirt, etc. Topical antibiotics are another popular prescription treatment for acne. Today, pledgettes containing topical antibiotics such as clindamycin and erythromycin are widely used for both their convenience, as well as their safety and efficacy.

While benzoyl peroxide would also be an ideal agent to incorporate into pledgettes for the treatment of acne, numerous attempts to incorporate benzoyl peroxide into pledgettes have been unsuccessful until the current invention. Since the benzoyl peroxide was not completely soluble in any of the vehicles tried, a considerable amount of the benzoyl peroxide was selectively "trapped" in the pledgette fibers, rendering the delivery of benzoyl peroxide to the skin uncertain. The applicant of this patent application had himself trial to produce benzoyl peroxide pledgettes several times in the 1980's and early 1990's without success for the very reason given above. However, surprisingly, the applicant has recently discovered a way or producing pledgettes such that the benzoyl peroxide is not selectively trapped in the pledgette material. I have found that by solubilizing benzoyl peroxide in vehicles containing moderate to high concentrations of acetone (from about 30% to 100%), pledgettes containing benzoyl peroxide in acetone compositions can be prepared such that the benzoyl peroxide is not selectively trapped in the pledgette. Consequently, the pledgette delivers the concentration of benzoyl peroxide contained in the acetone composition.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description of the invention and in the claims, all percentage amounts are stated in terms of weight percent (% w/w).

In accordance with this invention, compositions are provided whereby benzoyl peroxide is incorporated in vehicles containing about 30% to about 100% acetone so that the benzoyl peroxide is solubilized. Cloth pledgettes made of cotton, wool, nylon, rayon or other synthetic fabrics are then impregnated with such compositions and the resulting individual benzoyl peroxide pledgettes preferably are packaged in individual pouches, such as foil or plastic. Individual benzoyl peroxide pouches are then opened, the pledgette removed, and the pledgette rubbed across the surface of the face or other acne bearing area which the patient intends to treat for acne. Following use in this fashion, individual pledgettes are then discarded.

The instant invention thus relates to an article for use in the treatment of acne vulgaris, the article comprising a fiber pledgette impregnated with a composition comprising benzoyl peroxide and an amount of acetone sufficient to solubilize the benzoyl peroxide. Preferably, the pledgettes are packaged in individual pouches. The instant invention also comprises the method of manufacturing an article for use in the treatment of acne vulgaris comprising impregnating fiber pledgettes with a composition comprising benzoyl peroxide and an amount of acetone sufficient to solubilize the benzoyl peroxide, preferably packaging the pledgettes in individual pouches. The pouches can comprise known flexible, impermeable, sealable non-reactive materials such as aluminum foil, plastic film, or combinations of such materials.

The composition used to impregnate the cloth pledgette comprises benzoyl peroxide in the range of about 2–10%, and most preferably about 4.0–10%. Purified water is optionally present in an amount ranging from 0% to about 65%. Other optional ingredients include polyethylene glycol 400, which can be present in the range of about 0–15%, and glycerin which can be present in the range of about 0–20%. The balance of the composition is acetone. In a preferred embodiment the composition will comprise at least about 30% acetone.

The composition is prepared by blending the selected ingredients at ambient temperature until solubilization of the benzoyl peroxide is complete. Pledgettes of a desired fabric are then impregnated with the composition. Preferably, the pledgettes are packaged in individual pouches.

The following examples illustrate the present invention.

EXAMPLE 1

A composition comprising benzoyl peroxide 4.5%, acetone 69.0%, purified water 16.5%, and polyethylene glycol 400 10.0% was prepared and used to impregnate cotton pledgettes. Twenty-three acne patients ages 18–25 years applied the resulting product to their cheeks for five days with excellent results.

EXAMPLE 2

A composition comprising benzoyl peroxide 5.5%, acetone 67.0%, purified water 15.0%, and polyethylene glycol 400 12.5% was prepared and used to impregnate rayon pledgettes. Twenty-three acne patients ages 18–25 years applied the resulting product to the cheeks for five days with excellent results.

EXAMPLE 3

A composition comprising benzoyl peroxide 2.5%, acetone 35.0%, purified water 57.5%, and glycerin 5.0% was prepared and used to impregnate cotton pledgettes.

EXAMPLE 4

A composition comprising benzoyl peroxide 10.0%, acetone 88.2%, and purified water 1.8% was prepared and used to impregnate cotton pledgettes.

EXAMPLE 5

A composition comprising benzoyl peroxide 5.5%, acetone 73.5%, purified water 15.9%, and glycerin 5.0%. The resulting formulation was used to impregnate cotton pledgettes.

While the foregoing is a description of the preferred embodiments of the instant invention it will be readily apparent to those skilled in the art that various modifications may be made therein without departing from the true scope and spirit of the invention as set forth in the appended claims.

What is claimed is:

1. An article comprising a fiber pledgette impregnated with a liquid composition comprising about 2–10% benzoyl peroxide, at least about 30% acetone, water, and either polyethylene glycol or glycerine, the article being suitable for use in the application of benzoyl peroxide to the skin of a person afflicted with acne vulgaris for the treatment of acne vulgaris.

2. The article of claim **1** wherein said benzoyl peroxide is present in said solution in the amount of about 4.0–10%.

3. The article of claim **1** wherein said polyethylene glycol comprises polyethylene glycol 400.

4. The article of claim **3** wherein said polyethylene glycol 400 is present in said composition in an amount up to about 15%.

5. The article of claim **1** wherein said glycerin is present in said composition in an amount up to about 20%.

6. The article of claim **1** wherein said pledgette is made from a cloth containing fibers selected from the group consisting of cotton, wool, nylon, and rayon.

7. The article of claim **1** wherein said impregnated pledgette is packaged in an individual pouch.

8. The article of claim **7** wherein said pouch comprises foil.

9. The article of claim **7** wherein said pouch comprises plastic film.

10. A method of manufacturing an article for use in the treatment of acne vulgaris, the method comprising the steps of

(a) providing a liquid composition comprising about 2–10% benzoyl peroxide, about at least 30% acetone, water, and either polyethylene glcol or glycerine, and

(b) impregnating a fiber pledgette with said liquid composition, such that said impregnated fiber pledgette is suitable for use in the application of benzoyl peroxide to the skin of a person afflicted with acne vulgaris for the treatment of acne vulgaris.

11. The method of claim **10** wherein said composition is prepared with benzoyl peroxide present in the amount of about 4.0–10%.

12. The method of claim **10** wherein said polyethylene glycol comprises polyethylene glycol 400.

13. The method of claim **12** wherein said composition is prepared with polyethylene glycol 400 in an amount of up to about 15%.

14. The method of claim **10** wherein said composition is prepared with glycerin.

15. The method of claim **14** wherein said composition is prepared with glycerin in an amount of up to about 20%.

16. The method of claim **10** wherein said pledgette is made from a cloth containing fibers selected from the group consisting of cotton, wool, nylon, and rayon.

17. The method of claim **10** including the further step of packaging said pledgette in an individual pouch.

18. The method of claim **17** wherein said pouch comprises foil.

19. The method of claim **17** wherein said pouch comprises plastic film.

20. A method of treating acne vulgaris, the method comprising the steps of

(a) providing a fiber pledgette impregnated with a liquid composition comprising about 2–10% benzoyl peroxide, at least about 30% acetone, water, and either polyethylene glycol or glycerine, and

(b) using said impregnated fiber pledgette to apply benzoyl peroxide to the skin of a person afflicted with acne vulgaris.

21. The method of claim **20** wherein said benzoyl peroxide is present in said solution in the amount of about 4.0–10%.

22. The method of claim **20** wherein said polyethylene glycol comprises polyethylene glycol 400.

23. The method of claim **22** wherein said polyethylene glycol 400 is present in said composition in an amount up to about 15%.

24. The method of claim **20** wherein said glycerin is present in said composition in an amount up to about 20%.

25. The method of claim **20** wherein said pledgette is made from a cloth containing fibers selected from the group consisting of cotton, wool, nylon, and rayon.

26. The method of claim **20** wherein said impregnated pledgette is packaged in an individual pouch.

27. The method of claim **26** wherein said pouch comprises foil.

28. The method of claim **26** wherein said pouch comprises plastic film.

* * * * *

United States Patent [19]

Bernstein

[11] **4,416,886**

[45] **Nov. 22, 1983**

[54] **METHOD OF TREATING PRURITIS AND COMPOSITION THEREFOR**

[75] Inventor: **Joel E. Bernstein,** Deerfield, Ill.

[73] Assignee: **Dermall Limited,** Northbrook, Ill.

[21] Appl. No.: **288,166**

[22] Filed: **Jul. 29, 1981**

[51] **Int. Cl.**[3] **A61K 31/485**

[52] **U.S. Cl.** **424/260**

[58] **Field of Search** 424/260

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,181,726 1/1980 Bernstein 424/260

OTHER PUBLICATIONS

Chem. Abstr., vol. 77, Entry 105601q, (1972).

Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Emrich & Lee and Brown, Hill, Dithmar, Stotland, Stratman & Levy

[57] **ABSTRACT**

A topical treatment for relieving pruritis wherein naloxone, a pharmaceutically acceptable salt or a pharmaceutically acceptable chemical derivative is topically applied in a lotion, solution, cream or ointment.

9 Claims, No Drawings

METHOD OF TREATING PRURITIS AND COMPOSITION THEREFOR

BACKGROUND OF THE INVENTION

Itching or pruritis is a common dermatologic symptom. The causes of pruritis are complex and poorly understood. The best understood mechanism of itching is the release of histamine in the skin leading to urticarial wheals and intense itching. Such itching has traditionally been relieved by antihistamines. While antihistamine therapy is often effective, the sedation and drowsiness produced by antihistaminic agents limits their effectiveness.

Many kinds of itching are not however easily relieved by antihistamines. For example, conditions such as Hodgkin's Disease, mycosis fungoides (cutaneous malignacy) and severe jaundice produce intense itching unrelieved by antihistamines. Therefore, there is a need for improved treatment to relieve severe itching which can not only be an alternative to antihistaminic treatment of itching due to such causes as mosquitoe bites which responds to such treatment, but which further provides relief in intractable cases of pruritis which heretofore have been virtually impossible to treat except as disclosed in my prior U.S. Pat. No. 4,181,726 issued Jan. 1, 1980, a method based on the systemic effect on the central nervous system. The present invention provides such a composition and method independent of systemic effects on the central nervous system.

Naloxone is a narcotic antagonist which is not known to cause physical or psychological dependence and which exhibits essentially no pharmacological activity in non-addicts. Naloxone is normally given by injection to addicts to assist them in narcotic withdrawal and sometimes is administered to post operative patients for partial reversal of narcotic depression following the use of narcotics during surgery.

It has been found surprisingly that topical applications of naloxone are useful in alleviating severe itching in various conditions.

SUMMARY OF THE INVENTION

The present invention provides an improved composition and method of treating severe itching comprising topically administering a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable chemical derivative thereof to a mammalian patient in need of such treatment.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Naloxone hydrochloride is commercially available from Endo Laboratories, Inc., a subsidiary of the DuPont Company, 1000 Stewart Avenue, Garden City, N.Y. 11530. The preparation of naloxone is disclosed in U.S. Pat. No. 3,254,088.

The term pharmaceutically acceptable salts, as used herein, refers to the physiologically acceptable acid addition salts of naloxone such as the hydrochloride, hydrobromide, hydroiodide, acetate, valerate, oleate, etc.

Liquid dosage forms for topical administration includes acceptable emulsions, solutions and suspensions containing volatile diluents commonly used in the art, such as alcohol, glycol and the like. Besides such diluents, topically applied compositions may also include wetting agents, emulsifying and suspending agents.

In the practice of this invention naloxone in the form of a pharmaceutically acceptable salt such as the hydrochloride and pharmaceutically acceptable chemical derivatives thereof such as naltrexone which is the n-methyl cyclopropyl derivative are incororated into solutions, lotions, creams, and ointments for topical application in concentrations of from 0.01 to about 5 percent by weight. These topical products are applied to the skin 1 to 8 times daily. The relief experienced by those receiving the topical application was prompt although temporary.

EXAMPLE 1

1 percent by weight naloxone hydrochloride was incorporated into a solution composed of 70 percent by volume ethyl alcohol and 30 percent by volume propylene glycol and applied 6 times daily to 2 mosquito bites of less than 24 hours duration on a 11 year-old male. This child noted relief from his itching within 10 minutes of each application and the relief lasted 2–4 hours.

EXAMPLE 2

A 0.05% by weight naloxone hydrochloride was incorporated into Eucerin ® cream and applied 4 times daily to the body of a 60 year-old male with intractable itching due to mycosis fungoides. Eucerin ® cream is a synthetic lanolin containing cream produced by Beiersdorf, Inc. of South Norwalk, Conn. 06854. This was the first topical product the patient used that provided him with any significant relief from his itching.

EXAMPLE 3

An ointment composed chiefly of petrolatum and containing 0.01% by weight naloxone hydrochloride was applied 4 times daily to the body of a 60 year-old male with mycosis fungoides. Itching was diminished, although not as much as with the higher concentration of naloxone in Example 2.

EXAMPLE 4

0.1% by weight naloxone hydrochloride was incorporated into a zinc shake lotion and applied to the mosquitoe bites of a 6 year-old girl during a one month five interval in the summer. This lotion provided excellent relief from the itching.

EXAMPLE 5

5% by weight naloxone hydrochloride was incorporated into an ointment and applied 4 times daily for two days to a small eczematous patch on the left hand of a 38 year-old male. Itching was dramatically reduced by each application of the test ointment.

It will be apparent to those skilled in the art that only the preferred embodiments have been described by way of exemplification and that there are various modifications which fall within the scope of this invention.

I claim:

1. A method for relieving severe itching in patients in need of such treatment, said method comprising topically administering a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or naltrexone to a patient in need of such treatment.

2. The method of claim **1**, wherein said naloxone or pharmaceutically acceptable salt thereof or naltrexone is present in a solution, lotion, cream or ointment in the

range of between about .01 percent by weight to about 5 percent by weight.

3. The method of claim 1, wherein said naloxone or a pharmaceutically acceptable salt thereof or naltrexone is administered to a patient in need of such treatment periodically from 1 to 8 times per day.

4. The method of claim 1, wherein said pharmaceutically acceptable salt of naloxone is a physiologically acceptable acid addition salt.

5. The method of claim 1, wherein said pharmaceutically acceptable salt of naloxone is naloxone hydrochloride.

6. A composition of matter comprising a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or naltrexone in a lotion, cream or ointment suitable for topical use only.

7. The composition of claim 6, wherein naloxone or a pharmaceutically acceptable salt thereof or naltrexone is present in the lotion, cream or ointment in the range of between about 0.01 percent by weight to about 5 percent by weight.

8. The composition of claim 6, wherein the pharmaceutically acceptable salt of naloxone is a physiologically acceptable acid addition salt.

9. The composition of claim 8, wherein said salt is naloxone hydrochloride.

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[illegible]

United States Patent [19]

Bernstein et al.

[11] **Patent Number: 4,603,131**

[45] **Date of Patent: Jul. 29, 1986**

[54] **METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE MUCOUS MEMBRANES OF THE NOSE**

[76] Inventors: **Joel E. Bernstein**, 615 Brierhill Rd., Deerfield, Ill. 60015; **Clarence J. Endicott**, Abbott Laboratories, North Chicago, Ill. 60064

[21] Appl. No.: **372,231**

[22] Filed: **Apr. 26, 1982**

[51] **Int. Cl.**[4] **A61K 31/55**; A61K 31/135

[52] **U.S. Cl.** **514/220**; 514/654

[58] **Field of Search** 424/278, 244, 330; 514/220, 654

[56] **References Cited**

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3,144,442	8/1964	Schindler et al.	260/239
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Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—Ronald A. Sandler; Jerry A. Schulman

[57] **ABSTRACT**

A method and composition for preventing and treating irritation of the mucous membranes of the nose wherein a tricyclic anti-depressant topically applied to the nose is effective prophylactically to prevent irritation and a combination of the tricyclic anti-depressant with a vasoconstrictor is effective to prevent and to alleviate irritation of the mucous membranes of the nose.

24 Claims, No Drawings

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METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE MUCOUS MEMBRANES OF THE NOSE

BACKGROUND OF THE INVENTION

Allergic and irritant conditions of the mucous membranes of the nose are quite common and are treated with sympathomimetic amines applied locally to produce vasoconstriction of local blood vessels. Such irritation or allergies of the mucous membranes of the nose may follow introduction of foreign particles or chemical pollutants or may be part of the allergic manifestations of asthma, hayfever, and allergic rhinitis resulting in swollen mucous membranes, stuffiness and/or more or less continued discharge from the nose.

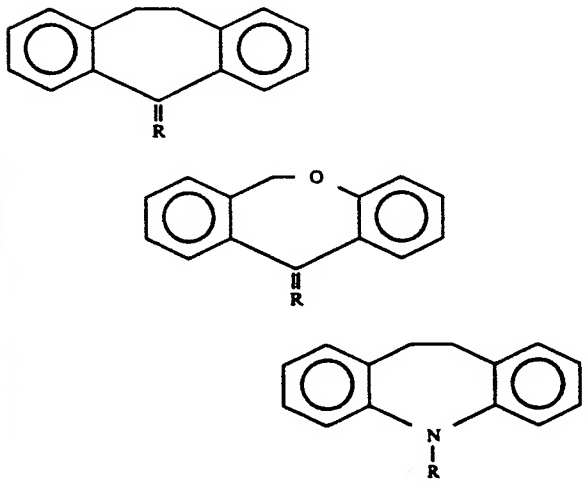
While there are a number of vasoconstrictive compounds available for treating irritation of the mucous membrane of the nose there are few effective compounds available for preventing irritation of the mucous membrane of the nose due to irritant and/or allergic conditions, that is there is no prophylactic treatment available.

We have discovered that tricyclic anti-depressants usually prescribed for ameliorating the effects of severe depression are prophylactically effective when applied topically to prevent irritation of the mucous membrane of the nose upon exposure to irritant conditions. These tricyclic anti-depressants alone have little effect on the treatment of already irritated mucous membranes, but when combined with known vasoconstrictors are effective for preventing future irritations while effectively treating present irritation.

SUMMARY OF THE INVENTION

The present invention relates to a method and composition for preventing and treating irritation of the mucous membranes of the nose.

A principal object of the present invention is to provide a method and composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of the nose a therapeutically effective amount of a tricyclic anti-depressant of the formula:

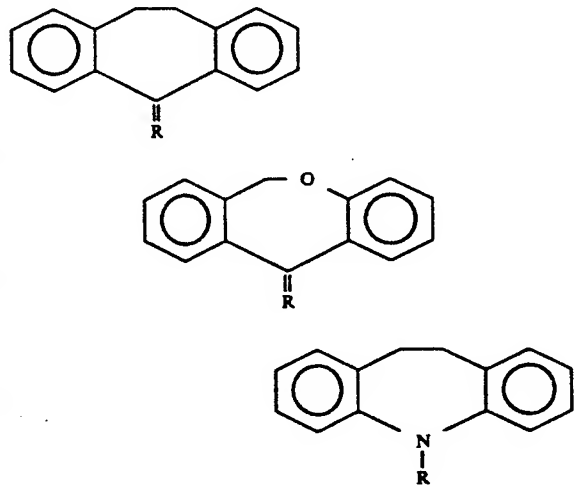


wherein R is an aliphatic secondary or tertiary amine.

Another object of the present invention is to provide a method of the type set forth wherein R is a secondary or tertiary amine connected to the ring structure by a three carbon chain.

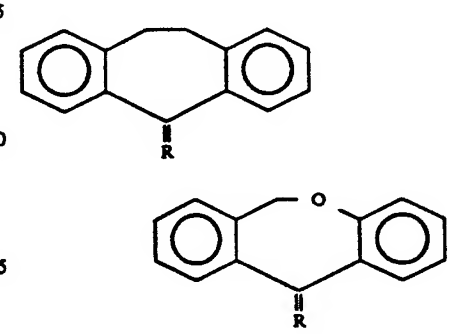
Yet another object of the present invention is to provide a method of the type set forth wherein the tricyclic anti-depressant is selected from the group consisting of imipramine, amitriptyline, doxepin, nortriptyline, protriptyline, desipramine and the acid addition salts thereof.

A further object of the present invention is to provide a method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of the nose a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine.

Still another object of the present invention is to provide a composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant selected from the group consisting of:



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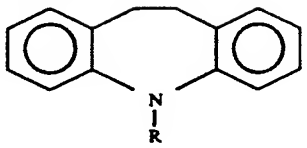
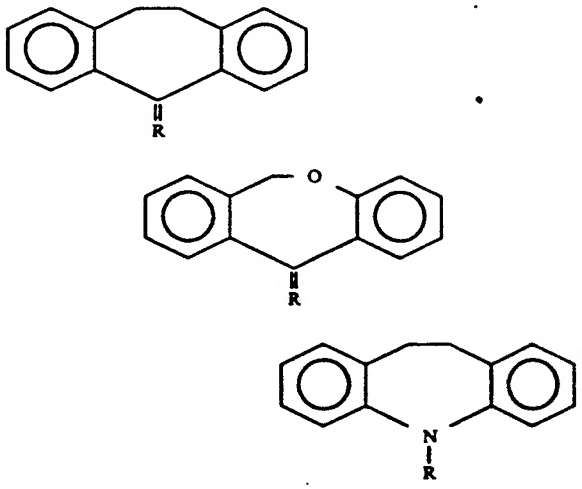


wherein R is an aliphatic secondary or tertiary amine in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of the composition in the range of from about 3 to about 7, the topical application of the composition to a mucous membrane of the nose prophylactically preventing the irritation.

A still further object of the present invention is to provide a composition of the type set forth wherein the tricyclic anti-depressant is selected from the group consisting of dibenzazepine, dibenzocycloheptadiene, dibenzoxepin, and derivatives thereof.

Yet another object of the present invention is to provide a composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7.

These and other objects of the present invention will be more readily understood when considered in conjunction with the following detailed description and examples.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

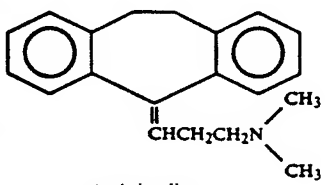
In the practice of this invention, nose drops are prepared employing 0.005% by weight to 1.25% by weight concentrations of the category of pharmacological agents known as the tricyclic anti-depressants, such as doxepin, amitriptyline and imipramine hydrochloride, respectively a tertiary amine derivative of dibenzoxepin, dibenzocycloheptadiene and dibenzazepine, in aqueous vehicles containing various viscosity adjusting agents, preservatives, tonicity adjusting agents, and buffering agents. Such nose drops are instilled from one to four times daily to prevent symptoms of nose irritation or allergy. Inclusion of known vasoconstrictor agents allows such drops to be used both prophylactically as well as therapeutically to relieve and prevent such nose irritation.

The preferred pH of the nose drop composition is in the range of from about 3 to about 7 and the buffering agents useful for obtaining said pH are sodium phosphate monobasic and sodium phosphate dibasic as well as citric acid, sodium citrate, acetic acid, sodium acetate, boric acid, sodium carbonate, sodium borate, hydrochloride acid and sodium hydroxide. Buffering agents may be present in the range of from about 0.1 to about 0.5% by weight of the composition but the pH is the controlled variable.

The tonicity agent is preferably sodium chloride and other pharmaceutically acceptable salts such as potassium chloride, calcium chloride, magnesium chloride and zinc sulfate. The osmotic agents such as sorbitol, dextrose and glycerin may also be used as tonicity agents. These osmotic agents also serve as humectant, emollient and flavoring agents. Certain aromatic oils may also be used as flavoring agents. The viscosity agent may be polyvinyl alcohol as well as methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers. The viscosity adjusting agents may be present in varying ranges from about 0.5% to about 2.5% by weight of the composition. The preservatives useful in the present invention include benzalkonium chloride, edetate disodium, sodium bisulfite, phenylmercuric acetate, cetylpyridinium chloride, thimerosal, chlorobutanol, cetyltrimethyl ammonium bromide, methylparaben, propylparaben and butylparaben usually present in the range of from about 0.01% to about 0.5% by weight of the composition.

The vasoconstrictors useful in the present invention are phenylephrine hydrochloride as well as the acid addition salts of tetrahydrozoline, xylometazoline, oxymetazoline, naphazoline, phenylephrine and ephedrine. The vasoconstrictors are generally present in the range of from about 0.01% to about 1.0%, depending on the vasoconstrictor used.

Although by way of example imipramine will be used in combination with other ingredients to illustrate the compositions and methods of the present invention, both tertiary and secondary amines of the tricyclic antidepressants are effective and are similar in their pharmacological action. The tertiary amines include amitriptyline, doxepin, and imipramine, respectively derivatives of dibenzocycloheptadiene, dibenzoxepin and dibenzazepine and have the following formulas:



Amitriptyline

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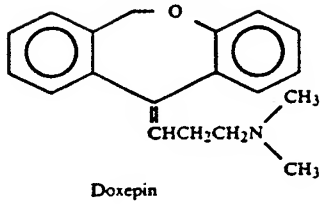
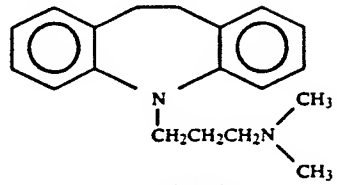
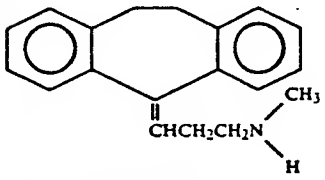


Doxepin

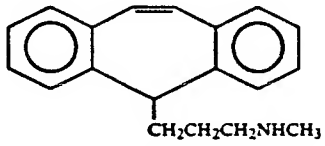


Imipramine

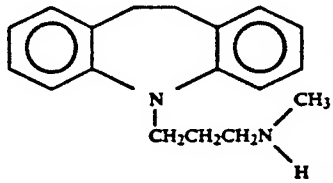
The secondary amines include nortriptyline, protriptyline and desipramine, respectively derivatives ot dibenzocycloheptadiene, dibenzoxepin and dibenzazepine and have the following formulas:



Nortriptyline



Protriptyline



Desipramine

The following Examples of the present invention are for purposes of illustration only and are effective for the prophylactic prevention of irritation of the mucous membrane of the nose when administered topically in divided doses from 1 to 4 times per day. The tricyclic anti-depressants, when combined with an appropriate vasoconstrictor, see Example VI, are effective in treating irritated mucous membranes as well as in preventing irritation.

EXAMPLE I

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol as an osmotic agent, flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% edetate disodium as preservatives; and 95.446% purified water. All percents are weight percents in all Examples.

EXAMPLE II

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol as an osmotic agent, flavorant, humectant and emollient; 1.5% polyvinyl alcohol as a viscosity adjuster; 0.1% benzalkonium chloride and 0.1% sodium bisulfite as preservatives; and 93.946% purified water.

EXAMPLE III

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 0.3% sodium chloride as a tonicity adjuster; 0.01% benzalkonium chloride, 0.1% edetate disodium as preservatives; and 99.146% purified water.

EXAMPLE IV

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 1.5% polyvinyl alcohol as a viscosity adjuster; 0.01% benzalkonium chloride, 0.1% edetate disodium and 0.1% sodium bisulfite as preservatives; 93.846% purified water.

EXAMPLE V

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% sodium bisulfite as preservatives; and 95.446% purified water.

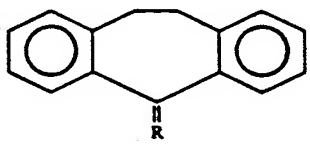
EXAMPLE VI

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% edetate disodium as preservatives; 95.20% purified water; and 0.25% phenylephrine hydrochloride as a vasoconstrictor.

All compositions are prepared at room temperature by conventional mixing techniques.

What is claimed is:

1. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic antidepressant selected from the group consisting of:



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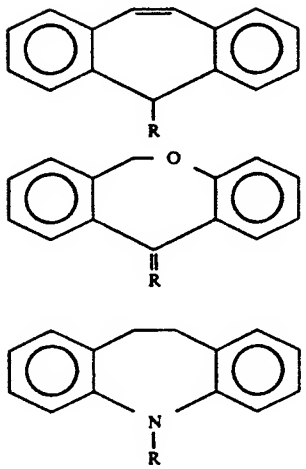

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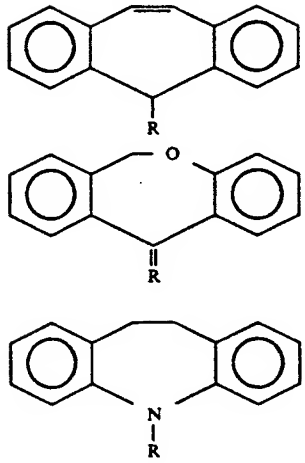


wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain.

2. The method of claim 1, wherein the tricyclic antidepressant is present in an aqueous carrier at a concentration of not less than about 0.005% by weight of the carrier.

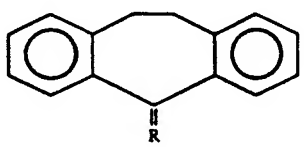
3. The method of claim 1, wherein the tricyclic antidepressant is present in an aqueous carrier at a concentration in the range of between about 0.05% by weight and about 0.005% by weight of the carrier.

4. The method of claim 1, wherein the tricyclic antidepressant is selected from the group consisting of the acid addition salts of imipramine, amitriptyline and doxepin.

5. The method of claim 1, wherein the tricyclic antidepressant is selected from the group consisting of nortriptyline, protriptyline and desipramine.

6. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic antidepressant selected from the group consisting of impipramine, amitriptyline, doxepin, nortriptyline, protriptyline, desipramine and the acid addition salts thereof.

7. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge as well as treating already irritated mucous membranes comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain.

8. The method of claim 7, wherein the tricyclic antidepressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic antidepressant in the carrier being not less than about 0.005% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

9. The method of claim 8, wherein the vasoconstrictor is present in the range of between about 0.01% by weight and about 1.0% by weight of the carrier.

10. The method of claim 8, wherein the anti-depressant is present in the range of between about 0.005% by weight and about 1.25% by weight of the carrier.

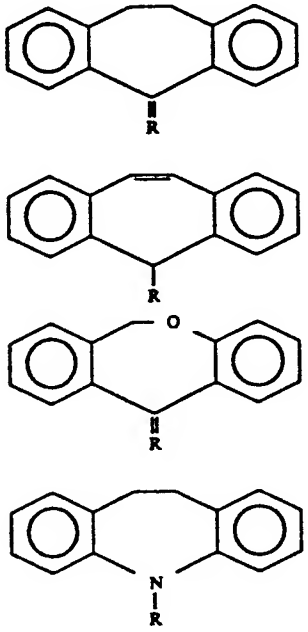
11. The method of claim 7, wherein the vasoconstrictor is selected from the group consisting of the acid addition salts of tetrahydrozoline, xylometazoline, oxymetazoline, phenylephrine and ephedrine.

12. The method of claim 11, and further comprising a pharmaceutically acceptable viscosity adjusting agent, a preservative, and a buffering agent, wherein the pH is maintained in the range of from about 3 to about 7.

13. The method of claim 12, wherein said vasoconstrictor is selected from the group consisting of phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, oxymetazoline hydrochloride, naphazoline hydrochloride, phenylephrine hydrochloride and ephedrine hydrochloride; wherein the viscosity adjusting agent is selected from the group consisting of polyvinyl alcohol, methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers; the preservative is selected from the group consisting of benzalkonium chloride, edetate disodium, sodium bisulfite, phenylmercuric acetate, cetylpyridinium chloride, thimerosal, chlorobutanol, cetyltrimethyl ammonium bromide, methylparaben, propylparaben and butylparaben; the buffering agent is selected from the group consisting of sodium phosphate monobasic, sodium phosphate dibasic, citric acid, sodium citrate, acetic acid, sodium acetate, boric acid, sodium carbonate, sodium borate, hydrochloric acid and sodium hydroxide.

14. A composition for preventing irritation of a mucous membrane of the nose cause by allergies, chemical pollutants, or physical irritants manifested by sneezing,

discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain in a suitable nasal fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7, and a flavoring agent the topical application of said composition being suitable for administration to a mucous membrane of the nose prophylactically preventing said irritation.

15. The composition of claim 14, wherein the tricyclic anti-depressant is present in an aqueous carrier at a concentration of not less than about 0.005% by weight of the carrier.

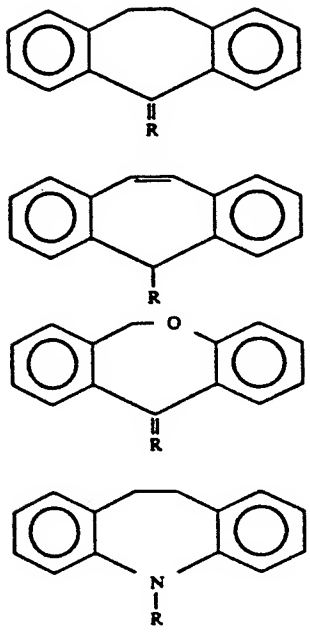
16. The composition of claim 14, wherein the tricyclic anti-depressant is present in an aqueous carrier at a concentration in the range of between about 0.005% by weight and about 1.25% by weight of the carrier.

17. The composition of claim 14, wherein the tricyclic anti-depressant is selected from the group consisting of the acid addition salts of imipramine, amitriptyline and doxepin.

18. The composition of claim 14, wherein the tricyclic anti-depressant is selected from the group consisting of nortriptyline, protriptyline and desipramine.

19. The composition of claim 14, and further comprising pharmaceutically acceptable viscosity agents, preservatives, buffers, and tonicity adjusting agents.

20. A composition for preventing irritation of a mucous membrane of the nose cause by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage as well as treating already irritated mucous membranes comprising a therapeutically effective amount of a tricyclic anti-depressant an effective amount of vasoconstrictor, and a flavoring agent wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7, the topical application of said composition being suitable for application to a mucous membrane of the nose prophylactically preventing said irritation.

21. The composition of claim 20, wherein the tricyclic anti-depressant is selected from the group consisting of imipramine, amitriptyline, doxepin, notriptyline, protriptyline, desipramine and the acid addition salts thereof.

22. The composition of claim 20, wherein the tricyclic anti-depressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic anti-depressant in the carrier being not less than about 0.005% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

23. The composition of claim 22, wherein the anti-depressant is present in the range of between about 0.005% by weight and about 1.25% by weight of the carrier and the vasoconstrictor is present in the range of between about 0.01% by weight and about 1.0% by weight of the carrier.

24. The composition of claim 22, and further comprising a pharmaceutically acceptable viscosity adjusting agent, a preservative and a buffering agent, wherein said vasoconstrictor is selected from the group consisting of phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, oxymetazoline hydrochloride, naphazoline hydrochloride, phenylephrine hydrochloride and ephedrine hydrochloride, the viscosity adjusting agent is selected from the group consisting of polyvinyl alcohol, methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers, the preservative is selected from the group consisting of benzalkonium chloride, edetate

United States Patent [19]

Bernstein

[11] **Patent Number: 4,505,909**

[45] **Date of Patent: Mar. 19, 1985**

[54] **METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE EYES**

[76] Inventor: **Joel E. Bernstein,** 615 Brierhill Rd., Deerfield, Ill. 60015

[21] Appl. No.: **425,126**

[22] Filed: **Sep. 27, 1982**

Related U.S. Application Data

[62] Division of Ser. No. 188,249, Sep. 17, 1980, Pat. No. 4,370,324.

[51] **Int. Cl.**[3] **A61K 31/33;** A61K 31/335; A61K 31/135

[52] **U.S. Cl.** **514/217;** 514/278; 514/450; 514/912; 514/656

[58] **Field of Search** 424/244, 278, 330

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Primary Examiner—Douglas W. Robinson

[57] **ABSTRACT**

A method and composition for preventing and treating irritation of the eyes wherein a tricyclic anti-depressant applied to the eyes is effective to prevent irritation and a combination of the tricyclic anti-depressant with a vasoconstrictor is effective to prevent and to alleviate irritation of the eyes.

17 Claims, No Drawings

METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE EYES

This is a division of application Ser. No. 188,249 filed Sept. 17, 1980, issued as U.S. Pat. No. 4,370,324 on Jan. 25, 1983.

BACKGROUND OF THE INVENTION

Allergic and irritant conditions of the conjunctivae and sclerae are quite common and are treated with sympathomimetic amines applied locally to produce vasoconstriction of local blood vessels. Such irritation or allergies of the mucous membranes of the eyes may follow accidental introduction of foreign particles or may be part of the allergic manifestations of asthma, hayfever, and allergic rhinitis.

While there are a limited number of vasoconstrictive compounds available for treating irritation of the eye there are no compounds available for preventing irritation of the eye due to irritant and/or allergic conditions, that is there is no prophylactic treatment available.

I have discovered that tricyclic anti-depressants usually prescribed for ameliorating the effects of severe depression are prophylactically effective when applied topically to prevent irritation of the eyes upon exposure to irritant conditions. These tricyclic anti-depressants have little effect on the treatment of already irritated eyes, but when combined with known vasoconstrictors are effective for preventing future irritations while effectively treating present irritation.

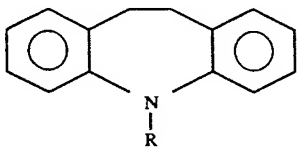
SUMMARY OF THE DISCLOSURE

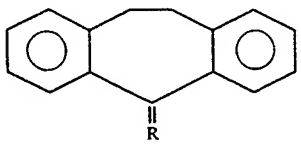
The present invention relates to a method and composition for preventing and treating irritation of the eyes.

A principal object of the present invention is to provide a method and composition for preventing irritation of the eyes due to allergic or irritant conditions comprising applying to the eyes a therapeutically effective amount of a tricyclic anti-depressant.

Another object of the present invention is to provide a method and composition for preventing and treating irritation of the eyes due to allergic or irritant conditions comprising periodically applying to the eyes a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor.

Yet another object of the present invention is to provide a method and composition for treating and preventing irritation of the eyes wherein the tricyclic anti-depressant contains one of the following ring structures:





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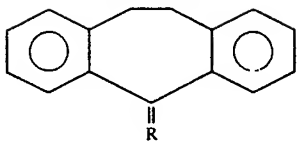


and also includes a viscosity adjusting composition, a preservative and a buffering agent.

These and other objects of the present invention may be more readily understood when considered in conjunction with the following detailed description and examples.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I investigated the possible local effects of tricyclic anti-depressant compounds usually used to ameliorate severe depression by instilling varying concentrations of these agents into the eyes of albino rabbits before and after instillation of 5-10% by weight solutions of sodium lauryl sulfate (SLS) in an aqueous/alcohol vehicle. The instillation of 5-10% by weight SLS solution produces marked irritation and injection of the rabbit sclerae and conjunctivae. Surprisingly, instillation of 0.05% by weight to 1% by weight of imipramine hydrochloride, amitriptyline hydrochloride, and doxepin hydrochloride protects the eye from the irritant effects of the SLS solution. However, these solutions provide only a little decrease in the eye irritation when instilled after irritation has been produced. When similar concentrations of these tricyclic anti-depressant compounds are combined with concentrations of 0.01% by weight to 0.05% by weight of known vasoconstrictors, such as naphazoline hydrochloride or tetrahydrozaline hydrochloride, the resulting opthalmic drops both reverse previously induced irritation and also render the eyes refractory to SLS for hours.

In the practice of this invention, eye drops are prepared employing 0.05% by weight to 1% by weight concentrations of the category of pharmacological agents known as the tricyclic anti-depressants, such as doxepin, amitriptyline and imipramine hydrochloride, respectively a tertiary amine derivative of dibenzoxepin, dibenzocycloheptadiene and dibenzazepine, in aqueous vehicles containing 0.05% hydroxypropyl methylcellulose as a viscosity adjusting agent, 0.01% benzalkonium chloride or 0.01% edetate sodium as preservatives and boric acid, sodium carbonate, and sodium hydroxide as buffering agents. Such eye drops are instilled from one to four times daily to prevent symptoms of eye irritation or allergy. Inclusion of known vasoconstrictor agents such as 0.01 to 0.05% naphazolixe hydrochlorides or tetrahydrozaline hydrochloride allows such drops to be used both prophylactically as well as therapeutically to relieve and prevent such eye irritation.

EXAMPLE I

A 0.05% doxepin hydrochloride solution containing 0.5% hydroxypropyl methlcellulose, 0.01% benzalkonium chloride, 1% sodium chloride and sodium carbonate and boric acid (utilized as buffers to adjust solution to a pH of 7.4) was instilled in the eyes of 5 albino rabbits. Five minutes after instillation of such drops, a 10% sodium lauryl sulfate (SLS) solution was instilled in the

rabbits' eyes. No injection of the sclerae or conjunctivae was noted during 30 minutes of observation.

EXAMPLE II

A 1.0% solution of amitriptyline hydrochloride containing 1.0% hydroxymethlcellulose, 0.1% edetate sodium, 1% potassium chloride, titrated with sodium borate and sodium hydroxide to a pH of 7.2 was instilled into the eyes of 5 albino rabbits 10 minutes prior to the introduction of 10.0% SLS into the rabbits' eyes. No eye irritation was noted in the 60 minutes of observation.

EXAMPLE III

A 0.5% solution of doxepin hydrochloride containing 2.5% hydroxypropyl methylcellulose, 0.004% benzalkonium chloride, 2.0% sodium chloride and sodium citrate and sodium carbonate as buffers (titrating eye drops to pH of 7.6) was instilled into the eyes of 4 albino rabbits. In 2 rabbits the drops were instilled 10 minutes before instillation of a 5% SLS solution and in the other 2, the drops were instilled 60 minutes after instillation of a 10% SLS solution. Instillation of the drops before the SLS prevented eye irritation. However, instillation after SLS had produced eye irritation resulted in no change or improvement in the eye irritation.

EXAMPLE IV

A 0.05% imipramine hydrochloride solution containing 0.01% hydroxymethylcellulose, thimerosal 0.005%, sodium chloride 0.5% (buffered to pH 7.0 with boric acid and sodium carbonate) was instilled into the eyes of 4 albino rabbits. Two rabbits received the eye drops 15 minutes before the instillation of 10% SLS, while 2 received the drops 90 minutes after the SLS was instilled. No irritation was observed in one rabbits' eyes and only mild irritation in the other rabbits' eyes, both of which had received the eye drops before SLS. The rabbits receiving SLS first had markedly irritated eyes with sclerae and conjunctival injection and this was not affected by the later instillation of the imipramine drops.

EXAMPLE V

A 0.05% amitriptyline hydrochloride solution, with 2.5% hydroxymethylcellulose, 0.01% edetate sodium, 0.5% sodium chloride, buffered to pH 7.4 by boric acid and sodium hydroxide, was instilled into the eyes of 5 rabbits on two separate days, on one day 10 minutes before the instillation of 10% SLS, while on the other day 60 minutes after SLS instillation. The amitriptyline drops prevented eye irritation from the SLS but had no effect on the irritation when instilled after the SLS.

EXAMPLE VI

An aqueous solution containing 1.0% doxepin hydrochloride, 0.05% naphazoline hydrochloride, 0.01% hydroxymethylcellulose, 0.004% benzalkonium chloride, 1.0% sodium chloride, buffered with sodium borate to pH 7.4 was instilled into the eyes of 5 albino rabbits on two different days. On one day the eye drops were instilled 10 minutes before the instillation of a 10% SLS solution and on the other day they were instilled 60 minutes after 10% SLS instillation. In the former case the drops prevented SLS-induced eye irritation, while in the latter the SLS-induced eye irritation was markedly reduced within ≡minutes and re-instillation of 10% SLS did not irritate the eyes again.

EXAMPLE VII

An aqueous solution of 0.05% amitriptyline hydrochloride and 0.01% naphazoline hydrochloride with 0.01% hydroxypropyl methylcellulose, 0.1% edetate sodium, 1% potassium chloride, buffered to pH 7.2 with boric acid and sodium hydroxide, was instilled into the eyes of 5 rabbits as described in Example VI. Prior instillation of these drops prevented or markedly reduced SLS induced eye irritation, while instillation after such irritation had been produced rapidly (within 5 minutes) reduced such irritation.

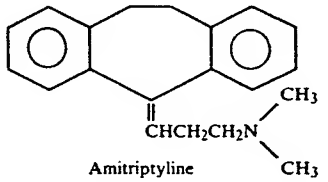
EXAMPLE VIII

A 0.01% amitriptyline hydrochloride solution containing 0.01% tetrahydrozaline hydrochloride, 0.01% hydroxymethycellulose, 0.01% benzalkonium chloride, 0.5% sodium chloride, buffered to pH 7.4 with sodium hydroxide and sodium citrate, was instilled as described in Example VI into the eyes of 5 rabbits on two separate occasions. Prior instillation of these drops prevented eye irritation from 10% SLS, while instillation after SLS-induced eye irritation, both relieved such irritation and prevented irritation from re-instillation of 10% SLS.

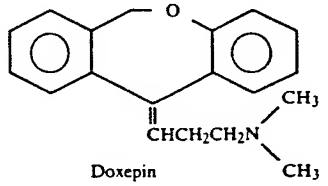
EXAMPLE IX

A 0.05% doxepin hydrochloride solution identical in composition to Example I but also containing 0.05% tetrahydrozaline hydrochloride was instilled into 4 rabbits eyes before and after SLS instillation on 2 different occasions. Prior instillation of these drops prevented or markedly reduced eye irritation in the rabbits' eyes. Instillation 60 minutes after SLS irritation was induced resulted in a prompt (within 10 minutes) clearing of the eyes and prevented irritation from the re-instillation of 10% SLS.

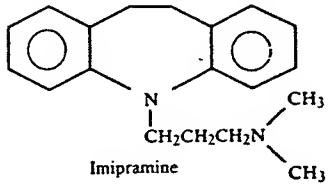
The tertiary amines have the following chemical formulas:



Amitriptyline



Doxepin

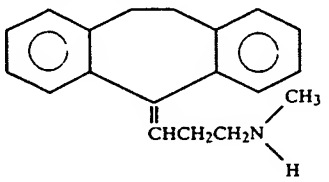


Imipramine

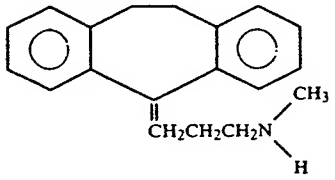
In addition, the secondary amines of the before mentioned tricyclics are effective and are included within

the scope of this invention. Secondary amines include Nortriptyline, Protriptyline and Desipramine, respectively derivatives of dibenzocycloheptadiene, dibenzoxepin and dibenzazepine, and have the following chemical formulas:

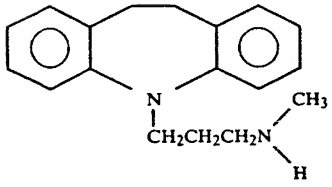
Nortriptyline



Protriptyline

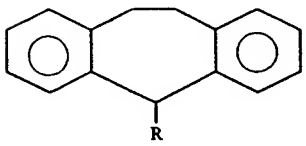


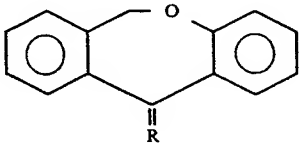
Desipramine

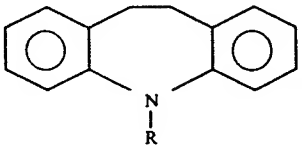


What is claimed is:

1. A method of preventing and treating irritation of the mucous membranes of the eye caused by allergies, chemical pollutants, or physical irritants, manifested by redness, tearing, burning, discomfort or itching, comprising applying topically to said eye a therapeutically effecive amount of a tricyclic anti-depressant selected from the group consisting of:







wherein R is an aliphatic secondary or tertiary amine having a three-aliphatic carbon chain connected to a nitrogen atom, with the seondary amine having the nitrogen atom attached to said chain and to one carbon atom, and with the tertiary amine having the nitrogen atom attached to said chain and to two carbon atoms; and

a therapeutically effective amount of an ophthalmically acceptable vasoconstrictor.

2. The method of claim 1, wherein the tricyclic anti-depressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic anti-depressant in the carrier being not less than about 0.05% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

3. The method of claim 2, wherein the vasconstrictor is present in the range of between about 0.01% by weight and about 0.05% by weight of the carrier.

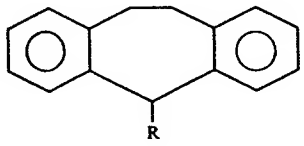
4. The method of claim 2, wherein the anti-depressant is present in the range of between about 0.05% by weight and about 1% by weight of the carrier.

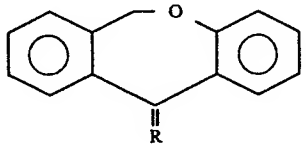
5. The method of claim 1, wherein the vasoconstrictor is naphazoline hydrochloride or tetrahydrozaline hydrochloride.

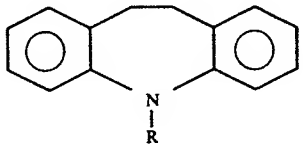
6. The method of claim 5, further comprising a viscosity adjusting agent, a preservative of benzalkonium chloride or edetate sodium and a buffering agent selected from boric acid, sodium carbonate, sodium hydroxide, or mixtures thereof.

7. The method of claim 6, wherein said viscosity adjusting agent is hydroxypropyl methylcellulose.

8. An ophthalmic composition for preventing and treating irritation of the mucous membrane of the eyes caused by allergies, chemical pollutants, or physical irritants, manifested by redness, tearing, burning discomfort, or itching, comprising a therapeutically effective amount of a tricyclic anti-depressant selected from the group consisting of:







wherein R is an aliphatic secondary or teritary amine having an aliphatic 3 carbon chain connected to a nitrogen atom, with the secondary amine having the nitrogen atom attached to said chain and to one carbon atom attached and with the teritary amine having the nitrogen atom attached to said chain and to two carbon atoms and

an ophthalmically acceptable vasoconstrictor,

said tricyclic anti-depressant and said vasoconstrictor in an ophthalmically suitable fluid carrier having an ophthalmically acceptable preservative and

buffering agent suitable to maintain said composition at a pH in excess of 7.

9. The composition of claim 8, wherein the tricyclic anti-depressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic anti-depressant in the carrier being not less than about 0.05% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

10. The composition of claim 9, wherein the vasoconstrictor is present in the range of between about 0.01% by weight and about 0.05% by weight of the carrier.

11. The composition of claim 9, wherein the anti-depressant is present in the range of between about 0.05% by weight and about 1% by weight of the carrier.

12. The composition of claim 8, wherein the vasoconstrictor is naphazoline hydrochloride or tetrahydrozaline hydrochloride.

13. The composition of claim 12, wherein said composition further comprises a viscosity adjusting agent, a preservative of benzalkonium chloride or edtate sodium and a buffering agent selected from boric acid, sodium carbonate, sodium hydroxide, or mixtures thereof.

14. The composition of claim 13, wherein the tricyclic anti-depressant is selected from the class consisting of dibenzazepine, dibenzocycloheptadiene, dibenzoxepin, and derivatives thereof.

15. The composition of claim 13, wherein the tricyclic anti-depressant is selected from the class consisting of imipramine hydrochloride, amitriptyline hydrochloride and doxepin hydrochloride.

16. The composition of claim 13, wherein the tricyclic anti-depressant is selected from the class consisting of nortriptyline, protriptyline, and desipramine.

17. The composition of claim 13, wherein said viscosity adjusting agent is hydroxypropyl methylcellulose.

* * * * *

United States Patent [19]

Bernstein

[11] **Patent Number: 4,486,450**

[45] **Date of Patent: Dec. 4, 1984**

[54] **METHOD OF TREATING PSORIATIC SKIN AND COMPOSITION**

[75] Inventor: **Joel E. Bernstein, Deerfield, Ill.**

[73] Assignee: **Dermalogical Enterprises, Ltd., Northbrook, Ill.**

[21] Appl. No.: **167,312**

[22] Filed: **Jul. 14, 1980**

[51] Int. Cl.³ **A61K 31/165**
[52] U.S. Cl. **424/324; 424/195**
[58] Field of Search 424/324, 195

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Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Ronald A. Sandler; Jerry A. Schulman

[57] **ABSTRACT**

A method and composition of treating psoriatic skin in which capsaicin is applied topically to the psoriatic skin in a pharmaceutically acceptable carrier wherein capsaicin is present in therapeutically acceptable concentrations of between about 0.01 and about 1 percent by weight. Subsequent exposure of the treated psoriatic skin to ultraviolet light in small doses aids treatment.

10 Claims, No Drawings

METHOD OF TREATING PSORIATIC SKIN AND COMPOSITION

BACKGROUND OF THE INVENTION

Psoriasis is a common chronic skin condition for which exist today a limited number of modestly effective agents, these being primarily topical corticosteroids and coal tar preparations. Various topical steroids effectively used to treat psoriasis of the skin includes fluocinolone acetonide, flurandrenolide, and triamcinolone acetonide are usually applied as creams or ointments. These topical steroids are most effective if covered with a polyethylene film which preferably is sealed with tape. Thin polyethylene gloves are used for treating the hands and fingers. Treatment of psoriatic skin can also include daily removal of the scales by applying soap and water and scraping gently with a soft brush, followed by the application of a keratolytic ointment.

I have observed psoriasis seems to be much less common in Mexicans and Orientals than in American Caucasians and Blacks. Mexicans and Orientals eat substantially more spicy food containing red pepper than either Caucasians or Blacks. Capsaicin (the active principle in red pepper that makes the red pepper hot) has been found to be an effective treatment for psoriasis of the skin when applied topically in divided doses. Exposure of the treated psoriatic skin to small doses of ultraviolet light also assists treatment.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating psoriatic skin and a composition therefor in which capsaicin is used as the principle therapeutic agent.

An important object of the present invention is to provide a method of treating psoriatic skin in human patients in need of such treatment comprising applying to the psoriatic skin a composition containing a therapeutically effective amount of capsaicin.

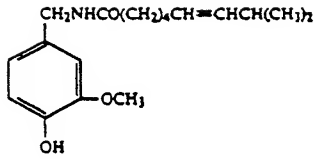
Another object of the present invention is to provide a method of treating psoriatic skin in human patients in need of such treatment comprising applying to the psoriatic skin a therapeutically effective amount of capsaicin and thereafter exposing the psoriatic skin to ultraviolet light.

A further object of the present invention is to provide an antipsoriatic composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of capsaicin.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In the practice of the present invention, capsaicin is distributed according to known techniques in various pharmaceutically acceptable carriers such as emulsions, solutions, suspensions including lotions, creams and ointments. Some of these carriers contain volatile diluents such as alcohol, glycol and the like and also may contain wetting agents, emulsifying and suspending agents.

Capsaicin the active ingredient in the psoriasis preparation is a pungent principle in fruit of the various species of Capsicum or Solanaceae (pepper plants). Chemically, Capsaicin is known as trans-8-methyl-N-vanillyl-6-nonenamide or (E)-N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonenamide. Its structure is:



Capsaicin, commercially available from the Sigma Chemical Company, is preferably present in the pharmaceutically acceptable carrier in an amount of not less than 0.01 percent by weight and is preferably present in the range of from about 0.01 percent by weight to about 1 percent by weight.

If capsaicin is present in the pharmaceutically acceptable carrier in an amount less than about 0.01 percent by weight, then there is insufficient concentration of the capsaicin to provide effective therapy. If the capsaicin is present in an amount greater than about 1 percent by weight of the pharmaceutically acceptable carrier, then the reaction of the psoriatic skin to the topical application is too painful. I have found the initial treatment of psoriatic skin with capsaicin results in an intense red painful reaction but the psoriatic skin becomes quite tolerant to capsaicin applications upon subsequent treatment.

After treatment of patients with capsaicin in a pharmaceutically acceptable carrier, exposure to small amounts of ultraviolet light in the range of between about 3 to 5 MED per exposure in some cases hastens clearing and produces a better therapeutic benefit than the use of capsaicin alone. MED stands for "Minimum Erythemal Dose", see the Handbook of Nonprescription Drugs, Sixth Edition, American Pharmaceutical Association, 1979. The capsaicin is preferably administered topically in divided doses 2 to 4 times a day with partial clearing of the psoriasis being observable in a five to ten day range.

The following examples further illustrate the present invention:

EXAMPLE 1

An ointment containing 0.01% by weight capsaicin was applied twice daily to the abdomen by a 28 year old white patient with extensive psoriasis involving most of the body. A plain emollient ointment was applied to the other areas of the skin. Within seven days of treatment the abdomen was nearly clear of psoriatic lesions, while the rest of the body was unchanged.

EXAMPLE 2

A 0.05% by weight capsaicin solution was applied to psoriatic elbow lesions of a 30 year old white patient with mild psoriasis limited to the elbows. The solution was applied 2 to 3 times daily. The patient was first observed again two weeks later and the elbows were completely clear of psoriatic lesions.

EXAMPLE 3

A cream having 0.1% by weight capsaicin was applied 3 times a day by a 25 year old white patient with psoriasis affecting primarily the extensor surfaces of the arms and legs. Within 7 days of application redness had decreased dramatically, scaling was reduced and the lesions had decreased significantly in size.

EXAMPLE 4

A 1% by weight solution of capsaicin was prepared in an aqueous/alcohol vehicle and applied 4 times daily to the arms, legs, chest and back of a 58 year old black patient with psoriasis. Almost complete resolution of the psoriatic lesions was observed after 5 days of such treatment.

EXAMPLE 5

A cream containing 0.1% by weight capsaicin was applied 4 times daily to the arms of a 49 year old white patient with psoriasis over the extensor surfaces of both arms. One arm was exposed to ultraviolet light for from 2 to 5 minutes in increasing doses every day for 8 days using a hot quartz lamp as the source of the ultraviolet light. After 8 days both arms were significantly improved. However, the arm exposed to ultraviolet light was completely clear of psoriatic lesions, while the other arm still had some small lesions.

EXAMPLE 6

A 0.5% by weight capsaicin ointment was applied twice daily by a 42 year old black patient with psoriasis involving the arms, legs, back, abdomen, and buttock. After 1 week the patient showed significant clearing of the lesions and at this time exposure to small (2–3 minutes) of ultraviolet light was initiated daily with resulting total clearing noted by the end of the following week.

It will be apparent to those skilled in the art that only the preferred embodiments have been described by way of exemplification and that there are various modifications and alterations therein which fall in the scope of this invention and are intended to be covered by the claims appended hereto.

What is claimed is:

1. A method of treating psoriatic skin in human patients in need of such treatment comprising applying to the psoriatic skin a therapeutically effective amount of capsaicin.

2. The method of claim 1, wherein the capsaicin is present in a pharmaceutically acceptable carrier and in an amount not less than about 0.01 percent by weight of the carrier.

3. The method of claim 1, wherein the capsaicin is present in the carrier in the range of from about 0.01 percent to about 1 percent by weight of the carrier.

4. The method of claim 1, wherein the capsaicin is applied topically in divided doses.

5. A method of treating psoriatic skin in human patients in need of such treatment comprising applying to the psoriatic skin a therapeutically effective amount of capsaicin, and thereafter exposing the psoriatic skin to ultraviolet light.

6. The method of claim 5, wherein the capsaicin is present in a pharmaceutically acceptable carrier and in an amount not less than about 0.01 percent by weight of the carrier.

7. The method of claim 6, wherein capsaicin is present in the carrier in the range of from about 0.01 percent to about 1 percent by weight of the carrier.

8. The method of claim 5, wherein the amount of ultraviolet light per exposure is in the range of from about 3 MED to about 5 MED.

9. An antipsoriatic composition comprising a pharmaceutically acceptable carrier of a cream or ointment and capsaicin present in an amount not less than about 0.01 percent by weight of the carrier.

10. The composition of claim 9, wherein said capsaicin is present in the range of from about 0.01 to about 1 percent by weight of said carrier.

* * * * *

METHOD OF TREATING ACNE VULGARIS AND COMPOSITION

RELATED APPLICATION

This is a continuation-in-part of my copending application Ser. No. 31,535, filed Apr. 19, 1979, now abandoned.

BACKGROUND OF THE INVENTION

Acne vulgaris is an inflammatory disease of the sebaceous glands characterized by an eruption of the skin, often pustular in nature but not suppurative. Acne is a common affliction of the adolescent and affects a small but significant percentage of the adult population. Acne involvement results in unslightly lesions, particularly on the face, and in some cases results in severe scarring.

There are a variety of methods for treating acne vulgaris including topically applying various scrubbing or abrasive compositions, topically applying deep cleaning or astringent compositions and also applying ultraviolet radiation. Nevertheless, acne vulgaris is seldom cured and only can be contained with difficulty.

Nicotinic acid and nicotinamide, water soluble vitamins, whose physiological active forms nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) serve a vital role as coenzymes in a variety of important metabolic reactions. Nicotinic acid is an essential dietary constituent, the lack of which leads to pellagra, a condition characterized by an erythematous skin eruption as well as gastrointestinal and neurological symptoms. Nicotinic acid and nicotinamide have been used routinely to treat pellagra for which they are therapeutic.

Nicotinic acid as well as nicotinamide are available from a variety of pharmaceutical houses such as Armor Pharmaceutical Company located in Phoenix, Ariz.; Brown Pharmaceutical Company Inc. located in Los Angeles, Calif.; and Keith Pharmaceutical Inc. located in Miami, Fla.

Although the above noted uses for nicotinic acid and nicotinamide are well documented, in addition, these vitamins have been used unsuccessfully in treatment of schizophrenia and atherosclerotic heart disease.

I have found surprisingly that nicotinic acid and nicotinamide are useful in the treatment of acne vulgaris by administering a therapeutically amount either topically or orally; I have also found that combinations of nicotinic acid and nicotinamide with certain chemical agents known to be effective in treating acne are more effective in treating acne than would be expected by treatment with the individual agents themselves. Such formulations include combinations of nicotinic acid or nicotinamide and sulfur, salicylic acid, benzoyl peroxide, vitamin A acid, erythromycin base, clindamycin phosphate and tetracycline hydrochloride.

SUMMARY

The present invention provides an improved method of and composition for the treatment of acne vulgaris involving the periodic application of an effective amount of nicotinic acid or nicotinamide or combination thereof with sulfur, salycylic acid, benzoyl peroxide, vitamin A, acid, erythromycin base, clindamycin phosphate and tetracycline hydrochloride.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In the practice of this invention, nicotinic acid or nicotinamide is administered orally in doses of 100 to 600 milligrams (mg) per day in divided doses taken 2 to 4 times per day. Also useful are topical solutions of nicotinamide and nicotinic acid in various organic vehicles such as a combination of ethyl alcohol and propylene glycol in which the active ingredient is present in the range of from about 1% to about 7% by volume of the carrier.

Additionally topical solutions of nicotinic acid or nicotinamide in various organic carriers in concentrations ranging ffrom 1 to 10% by volume of the carrier are incorporated into various organic vehicles including solutions, lotions, creams, gels, and ointments along with one or more of the following ingredients: sulfur in concentrations of 0.5% to 10% by volume; salicylic acid in concentrations of 0.5% to 10% by volume; benzoyl peroxide in concentrations of 5 to 10% by volume; vitamin A acid in concentrations from 0.01% to 0.5% by volume; erthromycin base in concentrations of from 1 to 5% by volume; clindamycin phosphate in concentrations from 1–5% by volume; tetracycline hydrochloride in concentrations from 1–5% by volume.

These applications, at least twice daily, resulted in a substantial and beneficial effect, that is a decrease in the inflammatory lesions such as papules, pustules, cysts but not comedones within approximately two weeks. The following examples illustrate the present invention.

EXAMPLE 1

100 milligrams of Nicotinic acid, obtained from the Armor Pharmaceutical Company, was orally administered to a 180 pound, 23 years old, male patient suffering from acne vulgaris. This patient received 3 oral doses of 100 milligrams of nicotinic acid 5–6 hours apart. These daily doses were required over a period of 14 days to observe a beneficial effect of a decrease in the inflammatory lesions.

EXAMPLE 2

100 milligrams of Nicotinamide, obtained from the Armor Pharmaceutical Company, was orally administered to a 120 pound, 21 years old, female patient suffering from acne vulgaris. This patient received 3 oral doses of 100 milligrams of nicotinamide, 5–6 hours apart. These daily doses were required over a period of 14 days to effect a decrease in inflammatory lesions.

EXAMPLE 3

600 milligrams of Nicotinic Acid, obtained from the Armor Pharmaceutical Company, was orally administered to a 160 pound, 24 year old, male patient suffering from acne vulgaris. This patient received 3 repeated doses, each being 200 milligrams of nicotinic acid, 5–6 hours apart. The daily dosage was repeated for 14 days before a decrease in the inflammatory lesions was noted.

EXAMPLE 4

600 milligrams of Nicotinamide, obtained from the Armor Pharmaceutical Company, was orally administered to a 160 pound, 28 years old, male patient suffering from acne vulgaris. This patient received 3 doses per day, each of 200 milligrams of nicotinamide, 5 hours apart. The daily dosage was repeated for 28 days before a decrease in the inflammatory lesions was noted.

EXAMPLE 5

Nicotinamide obtained from the Armor Pharmaceutical Comany was prepared with an ethyl alcohol carrier to form a 2% by volume solution of nicotinamide in alcohol. Twice daily topical treatments were administered to a 115 pound, 22 years old, female patient suffering from acne vulgaris. The topical treatments were administered 12–14 hours apart and this daily routine was repeated for a period of 14 days before a noticeable decrease in the inflammatory lesions occured.

EXAMPLE 6

A 5% by volume solution of nicotinamide in a 70% ethyl alcohol and 30% propylene glycol carrier was prepared. This solution was topically administered twice daily to a 170 pound, 24 years old, male patient suffering from acne vulgaris. The patient received topical treatments 12–14 hours apart and the daily treatments were repeated for 14 days before a noticeable reduction in the inflammatory lesions occured.

EXAMPLE 7

A 2% solution of nicotinic acid in an alcohol carrier was prepared. Twice daily topical applications were administered to a 150 pound, 27 years old, male patient suffering from acne vulgaris. The topical treatments were administered 12–14 hours apart and 28 days of treatment were required before a noticeable reduction in the inflammatory lesions occured.

EXAMPLE 8

A 5% solution of nicotinic acid in an alcohol-glycol carrier was prepared. Twice daily topical treatments of this solution were administered to a 118 pound, 24 years old, female patient suffering from acne vulgaris. The patient received two treatments 12–14 hours apart for a period of 14 days before a noticeable reduction in the inflammatory lesions occured.

The following examples illustrate a variety of combinations of nicotinamide and nicotinic acid with other chemical agents known to be effective against acne vulgaris. I have utilized these combinations in potassium-iodide-induced inflammation of the skin, a model that closely simulates acne vulgaris.

EXAMPLE 9

Solutions containing 1%, 5%, and 10% nicotinamide or nicotinic acid, acid, and 0.5%, 2%, 5%, and 10% sulfur were prepared in 2 vehicles, 1 containing 70% ethanol and 30% propylene glycol and the other containing 60% ethanol, 10% propylene glycol and 1% laureth—4. The solutions were applied to small areas on the backs of 10 normal volunteers aged 21–30 years and after drying patches containing 40% potassium-iodide (KI) were applied. Control patches had only the vehicle alone applied. The patches were read 48 hours after application. All combinations of nicotinamide or nicotinic acid with sulfer were dramatically effective at blocking the acneform papules and pustules which developed in the control areas.

EXAMPLE 10

Vehicles containing 1%, 5%, and 10% nicotinamide and 0.5%, 2%, 6% and 10% salicylic acid were prepared and applied on the backs of 10 volunteers in order to evaluate suppression of KI-induced acne form lesions. The vehicles included a gel containing 60% propylene glycol, 19.4% ethyl alcohol, hydroxypropyl cellulose and water, and a solution containing 70% ethyl alcohol and 30% propylene Glycol. All combinations of nicotinamide and salicylic acid suppressed acne lesions in the test areas, with suppression being complete in the combinations containing more than 2% salicylic acid.

EXAMPLE 11

1,2,5, and 10% concentrations by volume of nicotinic acid and nicotinamide were incorporated into gels containing 5% and 10% concentrations of benzoyl peroxide. These gels also contained 37% ethanol, 6% laureth—4, carbomer 940, di-isopropanolamine, disodium edetate and water. These gels were applied to the backs of 20 volunteers and acneform eruptions were induced in the test areas with KI and 10% crude coal tar under occlusion. Combinations of the nicotinic acid or nicotinamide and benzoyl peroxide were quite effective in suppressing the resulting "acne", and the combination products were especially active in the coal tar assay.

EXAMPLE 12

2% and 5% concentrations of nicotinamide were incorporated into gel and cream vehicles containing 0.025%, 0.05% or 0.1% by volume vitamin A acid and tested in the previously described inflammatory acne models and compared to vehicle controls. The combinations offered impressive suppression of KI and coal tar acnegenesis.

EXAMPLE 13

Solutions containing 70% ethanol, 30% propylene glycol were utilized as the vehicles for a series of acne treatment preparations containing 1%, 2%, 5%, and 10% concentrations by volume of nicotinic acid or nicotinamide and 1%, 2%, and 5% concentrations by volume of erythromycin base. Such combination formulations were dramatically effective at surpressing KI induced inflammation, although less potent against coal tar induced acnegenesis.

EXAMPLE 14

Ointments of white petrolatum were prepared containing 1%, 2%, 5% and 10% concentrations of nicotinic acid or nicotinamide combined with 1–5% concentrations of clindamycin phosphate by volume and applied to subjects' backs after induction of acneform papules and pustules with KI. These acne lesions cleared within 4 days with such treatment .

EXAMPLE 15

Tetracycline hydrochloride, in concentrations by volume of 1,2, and 5%, was incorporated in creams containing 1%, 2%, 5%, and 10% nicotinamide and applied to subjects' backs after induction of papules and pustules by KI. Acne lesions cleared within 5 days. However, a slight yellow staining of the skin was noted in the treatment areas.

EXAMPLE 16

A solution containing 70% ethanol and 30% propylene glycol was utilized to prepare acne treatment preparations containing 1%, 2%, 5% and 10% nicotinamide and combinations of sulfur and salicylic acid by volume as follows: 0.5% sulfur, 2% salicylic acid; 2% sulfur, 2% salicylic acid; 5% sulfur, 5% salicylic acid. These solutions were utilized in suppressing KI-induced in-

flammation and provided slightly superior acne suppressive effects than the combination of just nicotinamide and sulfur or nicotinamide and salicylic acid.

The present invention includes within the scope thereof pharmaceutical compositions suitable for both topical and oral administration having as an active ingredient thereof nicotinic acid or nicotinamide. Also included in the scope of the invention is the combination of nicotinic acid or nicotinamide with one or more of sulfur, salicylic acid, benzoyl peroxide, vitamin A acid, erythromycin base, clindamycin phosphate and tetracycline hydrochloride. Where appropriate a pharmaceutically acceptable carrier or diluent is employed.

Solid dosage froms for oral administration where applicable include capsules, tablets, pills, powders and granules. In such dosage forms, the active compound is admixed with at least one inert diluent such as sucrose, lactrose or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, granules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric codings, if desired.

Liquid dosage forms for oral administration where applicable include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants such as wetting agents, emulsifying agents, suspending agents, sweetening, flavoring and performing agents.

Liquid dosage forms for topical administration includes acceptable emulsions, solutions and suspensions containing volatile diluents commonly used in the art, such as alcohol, glycol and the like. Beside such diluents, topically applied compositions may also include wetting agents, emulsifying and suspending agents.

It will be apparent to those skilled in the art that only the preferred embodiments have been described by way of exemplification and that there are various modifications and alterations therein which fall in the scope of this invention and are intended to be covered by the claims appended hereto.

What is claimed is:

1. A method of decreasing the inflammatory lesions of acne vulgaris in human patients having such inflammatory lesions, said method comprising administering a therapeutically effective amount of nicotinamide to a patient having such inflammatory lesions.

2. The method of claim **1**, wherein said administration is topical with the effective ingredient being dispersed in a pharmaceutically acceptable carrier.

3. The method of claim **2**, wherein the effective ingredient is nicotinamide present in the amount of not less than about 1% by volume.

4. The method of claim **2**, wherein the effective ingredient is nicotinamide present in the range of between about 1% and about 7% by volume.

5. The method of claim **2**, wherein the carrier is selected from an alcohol or a glycol or mixtures thereof.

6. The method of claim **1**, wherein administration is by the oral route.

7. The method of claim **6**, wherein the effective ingredient is present in an amount in the range of between 100 mg. and 600 mg. per day administered in divided doses.

8. A method of decreasing the inflammatory lesions of acne vulgaris in human patients having such inflammatory lesions, said method comprising topically administering a therapeutically effective amount of nicotinamide in combination with one or more of sulfur, salicylic acid, benzoyl peroxide, vitamin A acid, erythromycin base, clindamycin phosphate and tetracycline hydrochloride to a patient having such inflammatory lesions.

9. The method fo claim **8**, wherein the effective ingredient is dispersed in a pharmaceutically acceptable carrier.

10. The method of claim **9** wherein the effective ingredient includes sulfur present in the range of from about 0.5% to about 10% by volume.

11. The method of claim **9** wherein the effective ingredient includes salicylic acid present in the range of from about 0.5% to about 10% by volume.

12. The method of claim **9** wherein the effective ingredient includes benzoyl peroxide present in the range of from about 5% to about 10% by volume.

13. The method of claim **9** wherein the effective ingredient includes vitamin A acid present in the range of from about 0.01% to about 0.5% by volume.

14. The method of claim **9** wherein the effective ingredient includes erythromycin base present in the range of from about 1% to about 5% by volume.

15. The method of claim **9** wherein the effective ingredient includes clindamycin phosphate present in the range of from about 1% to about 5% by volume.

16. The method of claim **9** wherein the effective ingredient includes tetracycline hydrochloride present in the range of from about 1% to about 5% by volume.

17. A topical composition effective in decreasing the inflammatory lesions of acne vulgaris in human patients having such inflammatory lesions, comprising a pharmaceutically acceptable carrier containing a therapeutically effective amount of nicotinamide in combination with a therapeutically effective amount of one or more of sulfur, salicylic acid, benzoyl peroxide, vitamin A acid, erythromycin base, clindamycin phosphate, and tetracycline hydrochloride.

18. The composition of claim **17** wherein the effective ingredient includes nicotinamide present in an amount not less than about 1% by volume.

19. The composition of claim **17** wherein the effective ingredient includes sulfur present in the range of from 0.5% to about 10% by volume.

20. The composition of claim **17** wherein the effective ingredient includes salicylic acid present in the range of from about 0.5% to about 10% by volume.

21. The composition of claim **17** wherein the effective ingredient includes benzoyl peroxide present in the range of from about 5% to about 10% by volume.

22. The composition of claim **17** wherein the effective ingredient includes vitamin A acid present in the range of from about 0.01% to about 0.5% by volume.

23. The composition of claim **17** wherein the effective ingredient includes erythromycin base present in the range of from about 1% to about 5% by volume.

24. The composition of claim **17** wherein the effective ingredient includes clindamycin phosphate present in the range of from about 1% to about 5% by volume.

25. The compostion of claim **17** wherein the effective ingredient includes tetracycline hydrochloride present in the range of from about 1% to about 5% by volume.

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United States Patent [19]

Bernstein et al.

[11] **Patent Number: 4,603,131**

[45] **Date of Patent: Jul. 29, 1986**

[54] **METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE MUCOUS MEMBRANES OF THE NOSE**

[76] Inventors: **Joel E. Bernstein**, 615 Brierhill Rd., Deerfield, Ill. 60015; **Clarence J. Endicott**, Abbott Laboratories, North Chicago, Ill. 60064

[21] Appl. No.: **372,231**

[22] Filed: **Apr. 26, 1982**

[51] **Int. Cl.**[4] **A61K 31/55**; A61K 31/135

[52] **U.S. Cl.** **514/220**; 514/654

[58] **Field of Search** 424/278, 244, 330; 514/220, 654

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Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—Ronald A. Sandler; Jerry A. Schulman

[57] **ABSTRACT**

A method and composition for preventing and treating irritation of the mucous membranes of the nose wherein a tricyclic anti-depressant topically applied to the nose is effective prophylactically to prevent irritation and a combination of the tricyclic anti-depressant with a vasoconstrictor is effective to prevent and to alleviate irritation of the mucous membranes of the nose.

24 Claims, No Drawings

METHOD AND COMPOSITION FOR TREATING AND PREVENTING IRRITATION OF THE MUCOUS MEMBRANES OF THE NOSE

BACKGROUND OF THE INVENTION

Allergic and irritant conditions of the mucous membranes of the nose are quite common and are treated with sympathomimetic amines applied locally to produce vasoconstriction of local blood vessels. Such irritation or allergies of the mucous membranes of the nose may follow introduction of foreign particles or chemical pollutants or may be part of the allergic manifestations of asthma, hayfever, and allergic rhinitis resulting in swollen mucous membranes, stuffiness and/or more or less continued discharge from the nose.

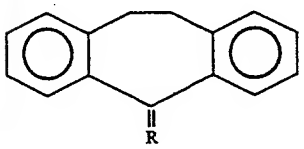
While there are a number of vasoconstrictive compounds available for treating irritation of the mucous membrane of the nose there are few effective compounds available for preventing irritation of the mucous membrane of the nose due to irritant and/or allergic conditions, that is there is no prophylactic treatment available.

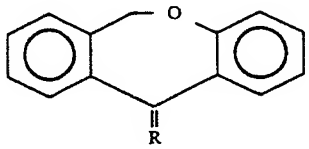
We have discovered that tricyclic anti-depressants usually prescribed for ameliorating the effects of severe depression are prophylactically effective when applied topically to prevent irritation of the mucous membrane of the nose upon exposure to irritant conditions. These tricyclic anti-depressants alone have little effect on the treatment of already irritated mucous membranes, but when combined with known vasoconstrictors are effective for preventing future irritations while effectively treating present irritation.

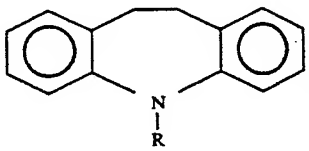
SUMMARY OF THE INVENTION

The present invention relates to a method and composition for preventing and treating irritation of the mucous membranes of the nose.

A principal object of the present invention is to provide a method and composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of the nose a therapeutically effective amount of a tricyclic anti-depressant of the formula:





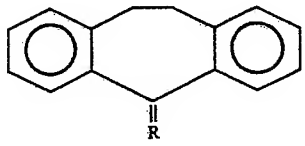


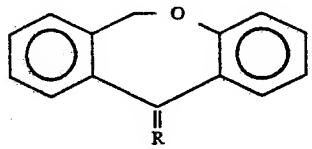
wherein R is an aliphatic secondary or tertiary amine.

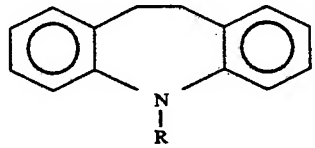
Another object of the present invention is to provide a method of the type set forth wherein R is a secondary or tertiary amine connected to the ring structure by a three carbon chain.

Yet another object of the present invention is to provide a method of the type set forth wherein the tricyclic anti-depressant is selected from the group consisting of imipramine, amitriptyline, doxepin, nortriptyline, protriptyline, desipramine and the acid addition salts thereof.

A further object of the present invention is to provide a method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of the nose a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:

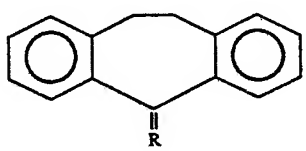


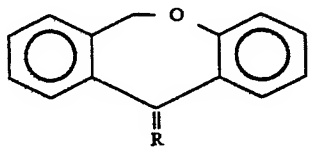




wherein R is an aliphatic secondary or tertiary amine.

Still another object of the present invention is to provide a composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant selected from the group consisting of:





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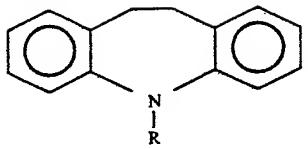
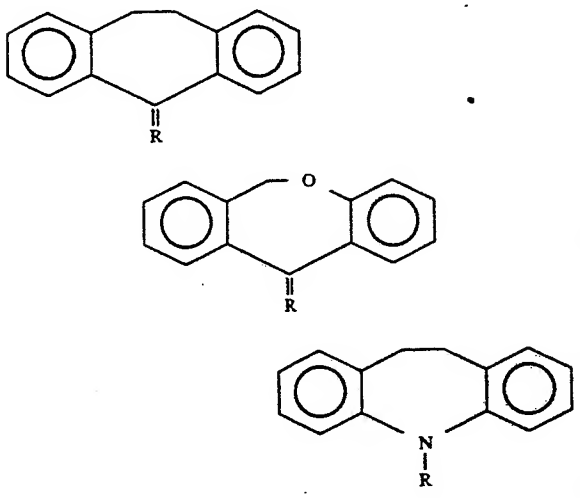


wherein R is an aliphatic secondary or tertiary amine in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of the composition in the range of from about 3 to about 7, the topical application of the composition to a mucous membrane of the nose prophylactically preventing the irritation.

A still further object of the present invention is to provide a composition of the type set forth wherein the tricyclic anti-depressant is selected from the group consisting of dibenzazepine, dibenzocycloheptadiene, dibenzoxepin, and derivatives thereof.

Yet another object of the present invention is to provide a composition for preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7.

These and other objects of the present invention will be more readily understood when considered in conjunction with the following detailed description and examples.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

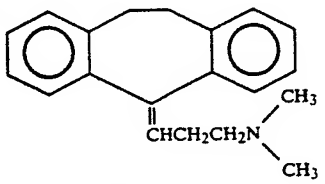
In the practice of this invention, nose drops are prepared employing 0.005% by weight to 1.25% by weight concentrations of the category of pharmacological agents known as the tricyclic anti-depressants, such as doxepin, amitriptyline and imipramine hydrochloride, respectively a tertiary amine derivative of dibenzoxepin, dibenzocycloheptadiene and dibenzazepine, in aqueous vehicles containing various viscosity adjusting agents, preservatives, tonicity adjusting agents, and buffering agents. Such nose drops are instilled from one to four times daily to prevent symptoms of nose irritation or allergy. Inclusion of known vasoconstrictor agents allows such drops to be used both prophylactically as well as therapeutically to relieve and prevent such nose irritation.

The preferred pH of the nose drop composition is in the range of from about 3 to about 7 and the buffering agents useful for obtaining said pH are sodium phosphate monobasic and sodium phosphate dibasic as well as citric acid, sodium citrate, acetic acid, sodium acetate, boric acid, sodium carbonate, sodium borate, hydrochloride acid and sodium hydroxide. Buffering agents may be present in the range of from about 0.1 to about 0.5% by weight of the composition but the pH is the controlled variable.

The tonicity agent is preferably sodium chloride and other pharmaceutically acceptable salts such as potassium chloride, calcium chloride, magnesium chloride and zinc sulfate. The osmotic agents such as sorbitol, dextrose and glycerin may also be used as tonicity agents. These osmotic agents also serve as humectant, emollient and flavoring agents. Certain aromatic oils may also be used as flavoring agents. The viscosity agent may be polyvinyl alcohol as well as methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers. The viscosity adjusting agents may be present in varying ranges from about 0.5% to about 2.5% by weight of the composition. The preservatives useful in the present invention include benzalkonium chloride, edetate disodium, sodium bisulfite, phenylmercuric acetate, cetylpyridinium chloride, thimerosal, chlorobutanol, cetyltrimethyl ammonium bromide, methylparaben, propylparaben and butylparaben usually present in the range of from about 0.01% to about 0.5% by weight of the composition.

The vasoconstrictors useful in the present invention are phenylephrine hydrochloride as well as the acid addition salts of tetrahydrozoline, xylometazoline, oxymetazoline, naphazoline, phenylephrine and ephedrine. The vasoconstrictors are generally present in the range of from about 0.01% to about 1.0%, depending on the vasoconstrictor used.

Although by way of example imipramine will be used in combination with other ingredients to illustrate the compositions and methods of the present invention, both tertiary and secondary amines of the tricyclic anti-depressants are effective and are similar in their pharmacological action. The tertiary amines include amitriptyline, doxepin, and imipramine, respectively derivatives of dibenzocycloheptadiene, dibenzoxepin and dibenzazepine and have the following formulas:



Amitriptyline

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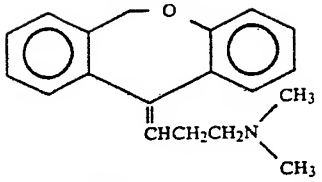
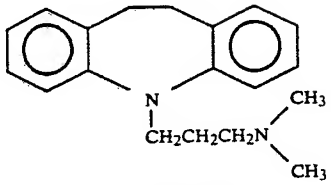
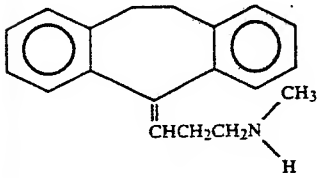


Doxepin

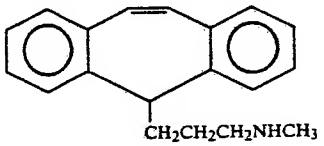


Imipramine

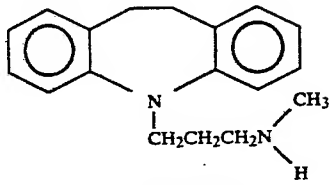
The secondary amines include nortriptyline, protriptyline and desipramine, respectively derivatives ot dibenzocycloheptadiene, dibenzoxepin and dibenzazepine and have the following formulas:



Nortriptyline



Protriptyline



Desipramine

The following Examples of the present invention are for purposes of illustration only and are effective for the prophylactic prevention of irritation of the mucous membrane of the nose when administered topically in divided doses from 1 to 4 times per day. The tricyclic anti-depressants, when combined with an appropriate vasoconstrictor, see Example VI, are effective in treating irritated mucous membranes as well as in preventing irritation.

EXAMPLE I

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol as an osmotic agent, flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% edetate disodium as preservatives; and 95.446% purified water. All percents are weight percents in all Examples.

EXAMPLE II

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol as an osmotic agent, flavorant, humectant and emollient; 1.5% polyvinyl alcohol as a viscosity adjuster; 0.1% benzalkonium chloride and 0.1% sodium bisulfite as preservatives; and 93.946% purified water.

EXAMPLE III

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 0.3% sodium chloride as a tonicity adjuster; 0.01% benzalkonium chloride, 0.1% edetate disodium as preservatives; and 99.146% purified water.

EXAMPLE IV

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 1.5% polyvinyl alcohol as a viscosity adjuster; 0.01% benzalkonium chloride, 0.1% edetate disodium and 0.1% sodium bisulfite as preservatives; 93.846% purified water.

EXAMPLE V

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% sodium bisulfite as preservatives; and 95.446% purified water.

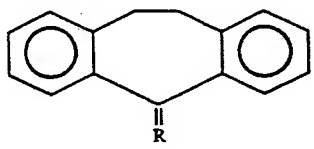
EXAMPLE VI

A composition consists of 0.05% imipramine hydrochloride; 0.368% sodium phosphate monobasic and 0.026% sodium phosphate dibasic as buffers; 4.0% sorbitol (osmotic agent), flavorant, humectant and emollient; 0.01% benzalkonium chloride and 0.1% edetate disodium as preservatives; 95.20% purified water; and 0.25% phenylephrine hydrochloride as a vasoconstrictor.

All compositions are prepared at room temperature by conventional mixing techniques.

What is claimed is:

1. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic antidepressant selected from the group consisting of:



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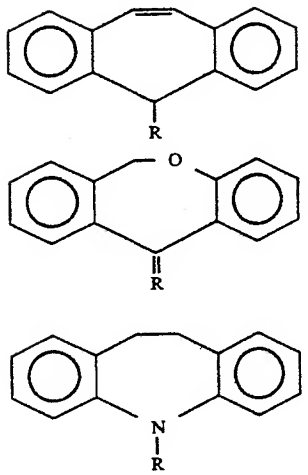

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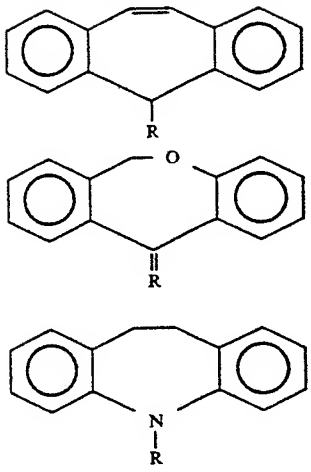


wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain.

2. The method of claim 1, wherein the tricyclic antidepressant is present in an aqueous carrier at a concentration of not less than about 0.005% by weight of the carrier.

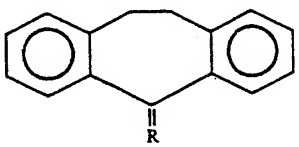
3. The method of claim 1, wherein the tricyclic antidepressant is present in an aqueous carrier at a concentration in the range of between about 0.05% by weight and about 0.005% by weight of the carrier.

4. The method of claim 1, wherein the tricyclic antidepressant is selected from the group consisting of the acid addition salts of imipramine, amitriptyline and doxepin.

5. The method of claim 1, wherein the tricyclic antidepressant is selected from the group consisting of nortriptyline, protriptyline and desipramine.

6. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic antidepressant selected from the group consisting of impipramine, amitriptyline, doxepin, nortriptyline, protriptyline, desipramine and the acid addition salts thereof.

7. A method of preventing irritation of a mucous membrane of the nose caused by allergies, chemical pollutants or physical irritants manifested by sneezing, discomfort, stuffiness or mucous discharge as well as treating already irritated mucous membranes comprising applying topically to a mucous membrane of said nose a therapeutically effective amount of a tricyclic anti-depressant and a vasoconstrictor wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain.

8. The method of claim 7, wherein the tricyclic antidepressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic antidepressant in the carrier being not less than about 0.005% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

9. The method of claim 8, wherein the vasoconstrictor is present in the range of between about 0.01% by weight and about 1.0% by weight of the carrier.

10. The method of claim 8, wherein the anti-depressant is present in the range of between about 0.005% by weight and about 1.25% by weight of the carrier.

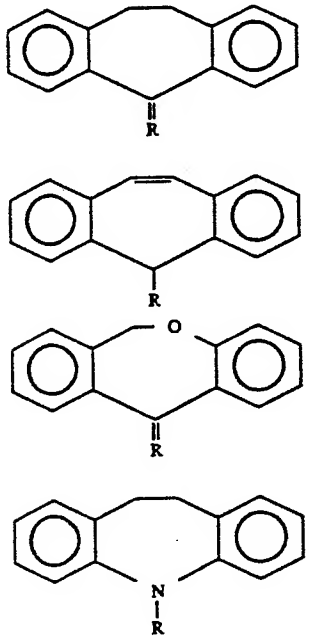
11. The method of claim 7, wherein the vasoconstrictor is selected from the group consisting of the acid addition salts of tetrahydrozoline, xylometazoline, oxymetazoline, phenylephrine and ephedrine.

12. The method of claim 11, and further comprising a pharmaceutically acceptable viscosity adjusting agent, a preservative, and a buffering agent, wherein the pH is maintained in the range of from about 3 to about 7.

13. The method of claim 12, wherein said vasoconstrictor is selected from the group consisting of phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, oxymetazoline hydrochloride, naphazoline hydrochloride, phenylephrine hydrochloride and ephedrine hydrochloride; wherein the viscosity adjusting agent is selected from the group consisting of polyvinyl alcohol, methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers; the preservative is selected from the group consisting of benzalkonium chloride, edetate disodium, sodium bisulfite, phenylmercuric acetate, cetylpyridinium chloride, thimerosal, chlorobutanol, cetyltrimethyl ammonium bromide, methylparaben, propylparaben and butylparaben; the buffering agent is selected from the group consisting of sodium phosphate monobasic, sodium phosphate dibasic, citric acid, sodium citrate, acetic acid, sodium acetate, boric acid, sodium carbonate, sodium borate, hydrochloric acid and sodium hydroxide.

14. A composition for preventing irritation of a mucous membrane of the nose cause by allergies, chemical pollutants, or physical irritants manifested by sneezing,

discomfort, stuffiness or mucous drainage comprising a therapeutically effective amount of a tricyclic anti-depressant selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain in a suitable nasal fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7, and a flavoring agent the topical application of said composition being suitable for administration to a mucous membrane of the nose prophylactically preventing said irritation.

15. The composition of claim **14**, wherein the tricyclic anti-depressant is present in an aqueous carrier at a concentration of not less than about 0.005% by weight of the carrier.

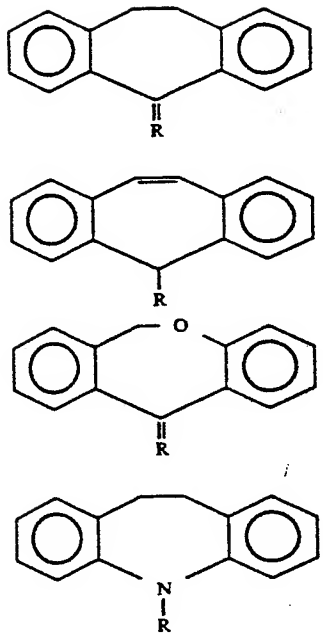
16. The composition of claim **14**, wherein the tricyclic anti-depressant is present in an aqueous carrier at a concentration in the range of between about 0.005% by weight and about 1.25% by weight of the carrier.

17. The composition of claim **14**, wherein the tricyclic anti-depressant is selected from the group consisting of the acid addition salts of imipramine, amitriptyline and doxepin.

18. The composition of claim **14**, wherein the tricyclic anti-depressant is selected from the group consisting of nortriptyline, protriptyline and desipramine.

19. The composition of claim **14**, and further comprising pharmaceutically acceptable viscosity agents, preservatives, buffers, and tonicity adjusting agents.

20. A composition for preventing irritation of a mucous membrane of the nose cause by allergies, chemical pollutants, or physical irritants manifested by sneezing, discomfort, stuffiness or mucous drainage as well as treating already irritated mucous membranes comprising a therapeutically effective amount of a tricyclic anti-depressant an effective amount of vasoconstrictor, and a flavoring agent wherein the tricyclic anti-depressant is selected from the group consisting of:



wherein R is an aliphatic secondary or tertiary amine connected to the ring by a three carbon chain in a suitable fluid carrier having an acceptable preservative and a buffering agent suitable to maintain the pH of said composition in the range of from about 3 to about 7, the topical application of said composition being suitable for application to a mucous membrane of the nose prophylactically preventing said irritation.

21. The composition of claim **20**, wherein the tricyclic anti-depressant is selected from the group consisting of imipramine, amitriptyline, doxepin, notriptyline, protriptyline, desipramine and the acid addition salts thereof.

22. The composition of claim **20**, wherein the tricyclic anti-depressant and the vasoconstrictor are present in an aqueous carrier, the concentration of the tricyclic anti-depressant in the carrier being not less than about 0.005% by weight of the carrier and the concentration of the vasoconstrictor in the carrier being not less than about 0.01% by weight of the carrier.

23. The composition of claim **22**, wherein the anti-depressant is present in the range of between about 0.005% by weight and about 1.25% by weight of the carrier and the vasoconstrictor is present in the range of between about 0.01% by weight and about 1.0% by weight of the carrier.

24. The composition of claim **22**, and further comprising a pharmaceutically acceptable viscosity adjusting agent, a preservative and a buffering agent, wherein said vasoconstrictor is selected from the group consisting of phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, oxymetazoline hydrochloride, naphazoline hydrochloride, phenylephrine hydrochloride and ephedrine hydrochloride, the viscosity adjusting agent is selected from the group consisting of polyvinyl alcohol, methyl cellulose, hydroxymethyl cellulose, hydroxy propylmethyl cellulose, carboxymethyl cellulose and other soluble polymers, the preservative is selected from the group consisting of benzalkonium chloride, edetate

United States Patent [19]

Bernstein

[11] Patent Number: 4,997,853

[45] Date of Patent: Mar. 5, 1991

[54] METHOD AND COMPOSITIONS UTILIZING CAPSAICIN AS AN EXTERNAL ANALGESIC

[75] Inventor: Joel E. Bernstein, Deerfield, Ill.

[73] Assignee: Galenpharma, Inc., Northbrook, Ill.

[21] Appl. No.: 501,424

[22] Filed: Mar. 28, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 279,587, Dec. 2, 1988, abandoned.

[51] Int. Cl.[5] A61K 31/16

[52] U.S. Cl. 514/626; 514/627

[58] Field of Search 514/626, 627

[56] References Cited

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4,599,342	7/1986	LaHann	514/627
4,628,063	12/1986	Haines	514/626
4,681,897	7/1987	Brand	514/627

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Jones, Day, Reavis & Pogue

[57] ABSTRACT

A method and composition for treating superficial pain syndromes incorporates capsaicin in a therapeutically effective amount into a pharmaceutically acceptable carrier and adding to this composition a local anesthetic such as lidocaine or benzocaine. The composition containing the anesthetic is then applied to the site of the pain. A variation on the treatment includes initial treatment with the composition containing the local anesthetic until the patient has become desenstitized to the presence of capsaicin and subsequent treatment with a composition ommitting the local anesthetic.

7 Claims, No Drawings

METHOD AND COMPOSITIONS UTILIZING CAPSAICIN AS AN EXTERNAL ANALGESIC

This application is a continuation of application Ser. No. 279,587 filed Dec. 12, 1988, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates generally to the treatment of superficial pain syndromes and, in particular, to improved uses of capsaicin to treat these conditions. Over the past 5 years topical capsaicin has emerged as the treatment of choice for superficial pain syndromes such as postherpetic neuralgia. See, for example, U.S. Pat. No. 4,536,404 entitled "Method and Composition for Treating Post-Herpetic Neuralgia", issued Aug. 20, 1985 to the inventor named herein. However, from 10% to 30% of patients treated with topical capsaicin experience moderate to severe local reactions, principally stinging or burning of the skin on initial applications. After a period of use, these reactions seem to fade. However, such burning may cause some of these patients to discontinue capsaicin use before they can experience pain relief from the treatment.

It has been discovered that incorporating topical anesthetics such as lidocaine (Entry 5310, p. 786, *Merck Index*, Tenth Edition 1983) and benzocaine (ethyl aminobenzoate, Entry 3710, p. 546, *Merck Index*, Tenth Edition 1983; into formulations containing capsaicin and then applying such formulations for the initial period of treatment can reduce or even eliminate the painful burning from the application of capsaicin, allowing the patient to continue therapy thereafter without requiring the use of anesthetics.

BRIEF DESCRIPTION OF THE INVENTION

In the practice of this invention topical anesthetics such as lidocaine and benzocaine in concentrations from 0.5% to 25% by weight are incorporated into pharmaceutically acceptable carriers such as creams, lotions, gels, ointments, suspensions and solutions containing capsaicin in a concentration of from about 0.01% to about 1% by weight and the resulting formulations are applied 2–6 times daily to the skin of patients with superficial pain disorders. In such a manner, the burning or stinging side effect of capsaicin therapy is reduced from a 10% to 30% incidence to an incidence level of less than 5%. Once the patient has become "desensitized" to the capsaicin, further therapy may be conducted by using the composition without the anesthetic.

DETAILED DESCRIPTON OF THE INVENTION

The following examples demonstrate the invention.

EXAMPLE 1

A cream containing 0.075% capsaicin was applied to the right flexor forearm of a patient four times over a 24 hour period. To the left flexor forearm of the same patient, a cream containing 0.075% capsaicin and 10% lidocaine was applied four times over the test period. The right arm became red and painful immediately at the site of application, and this burning pain decreased only slightly over the 24 hours of application. The left arm also became red at the application site, but only a slight stinging sensation was experienced at the application site on this arm, and after 24 hours no pain was experienced in the left arm.

EXAMPLE 2

A cream containing 0.025% capsaicin was applied to a single site on the right flexor forearm of a patient four times daily for 2 days. The left flexor forearm was treated in a similar fashion, but here a cream containing 0.025% capsaicin and 20% benzocaine was utilized. Intense burning pain was experienced immediately after cream applications to the right arm over the two days, but only moderate pain was experienced in the left arm on the first day and only slight pain in this arm on the second day.

While the foregoing describes the invention within the context of specific, preferred embodiments, it is to be understood that these embodiments, have been presented as example only and are not intended to limit the scope of the present invention. It is expected that others will perceive variations which, while differing from the foregoing, do not depart from the spirit and scope of the invention as herein described and claimed.

What is claimed is:

1. A method for treating superficial pain syndromes, said method comprising the step of topically applying to a patient having superficial pain, an effective amount of a composition comprising a therapeutically acceptable carrier and capsaicin, said capsaicin being present in a concentration, by weight, from about 0.01% to about 1.0%, said composition also including a topical anesthetic in a therapeutically effective amount, said anesthetic being present primarily to inhibit the local topical irritant effect of said capsaicin and whereby said capsaicin provides the primary relief for the pain syndrome.

2. The method of claim 1, wherein said topical anesthetic is lidocaine.

3. The method of claim 1 wherein said topical anesthetic is benzocaine.

4. The method of claim 1 including the further steps of:

(b) repeating the application of the composition until the capsaicin no longer produces an irritating or painful reaction; and

(c) applying subsequent applications of a composition containing only the therapeutically acceptable carrier and capsaicin and without any anesthetic.

5. A topical composition for the treatment of superficial pain syndromes, said composition comprising a therapeutically acceptable carrier, capsaicin in an amount of from about 0.01to 1.0% by weight, and a topical anesthetic in a therapeutically effective amount, said anesthetic being present primarily to inhibit the local topical irritant effect of said capsaicin when the composition is applied to a patient, whereby said capsaicin provides the primary relief of the pain syndrome.

6. The composition of claim 5, wherein said topical anesthetic is selected from the group consisting of lidocaine and benzocaine.

7. The composition of claim 6 wherein said topical anesthetic is present in a concentration from about 0.5% to about 25.0% by weight.

* * * * *

United States Patent [19]

Bernstein

[11] **Patent Number: 5,063,060**

[45] **Date of Patent: Nov. 5, 1991**

[54] **COMPOSITIONS AND METHOD FOR TREATING PAINFUL, INFLAMMATORY OR ALLERGIC DISORDERS**

[75] Inventor: **Joel E. Bernstein**, Deerfield, Ill.

[73] Assignee: **Cisco Limited Partnership**, Lincolnshire, Ill.

[21] Appl. No.: **452,476**

[22] Filed: **Dec. 19, 1989**

[51] **Int. Cl.**[5] **A61K 9/02**; A61K 9/20; A61K 1/48; A61K 31/16

[52] **U.S. Cl.** **424/422**; 424/436; 424/451; 424/464; 424/195.1; 514/627; 514/887; 514/914; 514/967

[58] **Field of Search** 424/422, 436, 451, 464, 424/195.1; 514/627, 887, 914, 937, 944, 967

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Primary Examiner—Thurman K. Page
Assistant Examiner—Amy Hulina
Attorney, Agent, or Firm—Jones, Day, Reavis & Pogue

[57] **ABSTRACT**

The invention relates to a method of treating painful, inflammatory or allergic disorders comprising treatment with an effective amount of a composition comprising cis-8-methyl-N-vanillyl-6-nonenamide. The invention also relates to compositions for use in the inventive method.

14 Claims, No Drawings

COMPOSITIONS AND METHOD FOR TREATING PAINFUL, INFLAMMATORY OR ALLERGIC DISORDERS

BACKGROUND OF THE INVENTION

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a compound derived from plants of the Solanacea family, commonly known as hot red peppers. Capsaicin has been utilized over the last two decades to study the neurophysiology and pharmacology of pain, as well as for the treatment of certain types of neuropathies and skin disorders. Such use is disclosed, for example, in U.S. Pat. No. 4,486,450, issued Dec. 4, 1984, and entitled "Method Of Treating Psoriatic Skil And Composition," and U.S. Pat. No. 4,536,404, issued Aug. 20, 1985, and entitled "Method And Composition For Treating Post-Herpetic Neuralgia;" both patents issued to the applicant herein.

While capsaicin is useful in treating painful neurological and other disorders, its utility has been limited by a troublesome adverse reaction which almost invariably accompanies its use. This reaction is a localized stinging and burning sensation, which can be quite severe, on application of capsaicin topically to skin or mucous membranes or on injection into tissues such as the dermis, the cerebrospinal canal or into blood vessels.

Attempts to reduce or eliminate this adverse effect have had only limited success, and include the incorporation of an anesthetic into the formulation. Since the stinging and burning have been thought to be directly linked to capsaicin's effects on neuropeptides in nerves, and these capsaicin effects on neuropeptides are thought to be crucial to capsaicin's efficacy in relieving pain, it has been considered impossible to significantly reduce the stinging and burning without greatly reducing or eliminating capsaicin's effectiveness.

When capsaicin is extracted from the pepper plant, such extracts contain a number of other compounds similar in structure to capsaicin, but with different properties. A number of these compounds, known as capsinoids, have been evaluated for their ability to deplete neuropeptides. None of these capsinoids has been found to be as effective as capsaicin in depleting the neuropeptides, and all of those known to have any measurable neuropeptide depleting activity also cause an uncomfortable degree of burning and stinging.

It is thus an object of the invention to provide methods of treating painful, inflammatory, or allergic disorders without the adverse stinging and burning associated with the use of capsaicin.

It is still another object of the invention to provide pharmaceutically acceptable compositions suitable for use in the inventive method.

In an attempt to discover a capsinoid which might be able to be more cheaply substituted for capsaicin in medicinal formulations, applicant has evaluated cis-8-methyl-N-vanillyl-6-nonenamide, a stereoisomer of capsaicin. The existence of this capsinoid in small quantities in pepper extracts has been known for some time. It has, however, always been believed that, like the other capsinoids, cis-8-methyl-N-vanillyl-6-nonenamide lacked significant neuropeptide depleting activity.

Applicant has discovered, quite surprisingly, that cis-8-methyl-N-vanillyl-6-nonenamide is much more potent as a depleter of neuropeptides from sensory nerves than is capsaicin. Even more surprisingly, applicant has discovered that cis-8-methyl-N-vanillyl-6-nonenamide produced such neuropeptide depletion without producing the extreme degree of burning or stinging produced by capsaicin. The invention therefore includes compositions of cis-8-methyl-N-vanillyl-6-nonenamide incorporated in topical formulations suitable for application to skin or mucous membranes, which compositions can produce in both man and animals pronounced analgesia without the pronounced irritant effects of capsaicin. The invention also includes compositions of cis-8-methyl-N-vanillyl-6-nonenamide incorporated into other medicinal formulations suitable for injection, oral ingestion, pulmonary inhalation, rectal administration or ophthalmic or nasal administration. When incorporated into such medicinal formulations, cis-8-methyl-N-vanillyl-6-nonenamide is substantially more potent than capsaicin and will produce less local irritation in the form of burning, stinging or vasodilitation than capsaicin. The invention also includes methods of using the inventive compositions to treat painful, inflammatory, or allergic disorders.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the invention, formulations are provided that incorporate cis-8-methyl-N-vanillyl-6-nonenamide into pharmaceutically acceptable vehicles suitable for use in man and animals. Such formulations include those for application to the skin, such as solutions, creams, ointments, gels, lotions, or pastes. Such formulation also include those for application to mucous membranes, including opthalmic and nasal solutions and suspensions, suppositories, and plasticized formulations suitable for oral and vaginal applications. Cis-8-methyl-N-vanillyl-6-nonenamide may also be formulated in sterile solutions or suspensions suitable for intradermal, subcutaneous, intramuscular, intravenous, or cerebrospinal injection. In each of the foregoing formulations, whether for application to the skin, application to the mucous membranes, or for injection, the cis-8-methyl-N-vanillyl-6-nonenamide may be present in the amount of about 0.001% to about 1.0% by weight, and preferably about 0.005% to about 0.25% by weight. The cis-8-methyl-N-vanillyl-6-nonenamide can be purchased from Eudora Research and Development Ltd., Sussex, United Kingdom.

Formulations within the scope of the invention also include those suitable for oral administration such as capsules, tablets, or liquid solutions or suspensions. In such formulations, the cis-8-methyl-N-vanillyl-6-nonenamide may be present in amounts of about 0.1–100.0 mg, and preferably about 0.5–50.0 mg, per tablet, capsule, or 5 ml dose of liquid solution or suspension.

Suitable pharmaceutical vehicles for the cis-8-methyl-N-vanillyl-6-nonenamide whether for topical application to skin or mucous membrane, injection, or oral administration, and methods of preparing such formulations as are within the scope of the invention, will be readily apparent to and understood by those skilled in the art.

The instant invention also comprises the method of applying, instilling, injecting, ingesting, or inhaling medicinal formulations containing cis-8-methyl-N-vanillyl-6-nonenamide in order to treat a wide range of painful and/or inflammatory disorders of man and animals such as neuropathies, skin disorders, arthritis, allergic disorders, and inflammatory bowel disorders.

The compositions of the instant invention and the methods of their use will be more readily comprehended from the following examples.

EXAMPLES

EXAMPLE 1

Cis-8-methyl-N-vanillyl-6-nonenamide was incorporated into a pharmacologically inert cream vehicle at a concentration of 0.025% and capsaicin was incorporated into the same cream vehicle at the identical concentration. The two creams were applied to 5 cm diameter patches on the forearms of 75 human volunteers under a randomized double-blind design. Each cream was applied 4 times over a 48 hour period and then the patients were examined. Stinging, burning and erythema were noted and rated for severity in each area. It was observed that while relatively frequent and severe local reactions were noted with capsaicin, the application of cis-8-methyl-N-vanillyl-6-nonenamide caused much less frequent, milder local reactions. Differences in both degree of stinging or burning and erythema noted between cis-8-methyl-N-vanillyl-6-nonenamide and capsaicin were statistically significant in favor of cis-8-methyl-N-vanillyl-6-nonenamide.

EXAMPLE 2

Male Sprague Dawley rats were prepared under halothane anesthesia with lumbar intrathecal catheters. After a 5-day period of recovery the rats received an intrathecal injection of either cis-8-methyl-N-vanillyl-6-nonenamide, capsaicin or a control vehicle and then nociception tested with a 49° C. hot plate. In this test performed 1, 3 and 7 days following treatment with cis-8-methyl-N-vanillyl-6-nonenamide, capsaicin, or control vehicle, the rats are placed on a surface maintained at 49° C. The anticipated endpoint is either a jump or a licking of the hindpaw. The latency to this response is measured. Failure to lick in 120 seconds is cause for termination of the test and assignment of that score. The results of this test showed that at doses of 1 and 10 ug, latencies of animals treated with cis-8-methyl-N-vanillyl-6-nonenamide were statistically significantly greater than those treated with capsaicin or the control vehicle.

EXAMPLE 3

The male Sprague Dawley rats of Example 2 were sacrificed 7 days following treatment, then decapitated, and the spinal cords rapidly removed by hydraulic pressure. Cords were frozen and then assayed for the neuropeptides substance P(SP) and Calcitonin Gene Related Peptide (CGRP). The injection of either cis-8-methyl-N-vanillyl-6-nonenamide or capsaicin resulted in dose dependent decreases in the levels of SP and CGRP in the dorsal but not ventral horns of the rat lumbosacral spinal cord. Cis-8-methyl-N-vanillyl-6-nonenamide was statistically significantly more potent than capsaicin in decreasing levels of SP. The two chemicals were equally effective in CGRP depletion.

EXAMPLE 4

Cis-8-methyl-N-vanillyl-6-nonenamide in a concentration of 0.075% was incorporated into the inert cream vehicle of Example 1 and applied four times daily to the chest of a patient with painful postherpetic neuralgia who had been unable to tolerate the burning produced by earlier applications of capsaicin. The patient experienced no burning or stinging on application of the cis-8-methyl-N-vanillyl-6-nonenamide cream and within 2 weeks noted marked reduction of his pain.

EXAMPLE 5

Using the same inert cream vehicle of Examples 1 and 4, vehicle cream containing 0.75% capsaicin and an identical vehicle cream containing 0.75% cis-8-methyl-N-vanillyl -6-nonenamide were applied to the right and left feet and legs respectively of a patient with symmetrical diabetic neuropathy. Both creams were applied three times daily for 4 weeks. At the end of this 4 week treatment period, the left leg which had been treated with the cis-8-methyl-N-vanillyl6-nonenamide cream was markedly less painful than prior to treatment, while the right leg which had been treated with capsaicin cream demonstrated moderate reduction in pain. The patient complained of slight stinging and burning for the first 5 days on application of capsaicin cream, but no stinging or burning at any time during application of the cis-8-methyl-N-vanillyl-6-nonenamide.

While the foregoing is a description of the preferred embodiments of the instant invention it will be readily apparent to those skilled in the art that various modifications may be made therein without departing from the true scope and spirit of the invention as set forth in the appended claims.

I claim:

1. A composition comprising cis-8-methyl-N-vanillyl-6nonenamide in an amount of about 0.001% to about 1.0% by weight and a pharmaceutically acceptable vehicle, said composition for use in the treatment of painful or allergic disorders, said composition being comparable in efficacy to compositions containing capsaicin but with significantly less local adverse effects normally associated with capsaicin.

2. The composition of claim **1** wherein said composition is suitable for application to the skin.

3. The composition of claim **2** wherein said vehicle is selected from the group consisting of a lotion, a solution, a cream, an ointment, a gel, or a paste.

4. The composition of claim **1** wherein said composition is suitable for application to mucous membranes.

5. The composition of claim **4** wherein said vehicle is selected from the group consisting of solutions, suspensions, suppositories, and plasticized formulations.

6. The composition of claim **1** wherein said composition is suitable for injection.

7. The composition of claims **1, 3, 5,** or **6** cis-8-methyl-N-vanillyl-6-nonenamide is present in the amount of about 0.005% to about 0.25% by weight.

8. A method of treating painful or allergic disorders comprising treatment with an effective amount of a composition containing cis-8-methyl-N-vanillyl-6-nonenamide in an amount of about 0.001% to about 1.0% by weight in a pharmaceutically acceptable vehicle, said composition being comparable in efficacy to compositions containing capsaicin but with significantly less local adverse effects normally associated with capsaicin.

9. The method of claim **8** wherein said method of treatment is selected from the group consisting of application of skin, application to mucous membrane and injection .

10. The method of claim **8** wherein said method cis-8-methyl-N-vanillyl-6-nonenamide is present in the amount of about 0.005–0.25% by weight.

11. A composition suitable for oral administration, comprising a pharmaceutically acceptable vehicle in the form of capsules, tablets, liquid solutions or suspensions and containing cis-8-methyl-N-vanillyl-6-nonenamide present in an amount of about 0.1–100.0 mg. per capsule, tablet, or 5 ml. portion of liquid, said composition being comparable in efficacy to compositions containing capsaicin but with significantly less local adverse effects normally associated with capsaicin.

12. The composition of claim 11 wherein cis-8-methyl-N-vanillyl-6-nonenamide is present in the amount of amount of 0.5–50.0 mg per capsule, tablet, or 5 ml portion of liquid.

13. A method of treating painful or allergic disorders by oral administration and comprising treatment with an effective amount of a composition containing cis-8-methyl-N-vanillyl-6-nonenamide in an amount of about 0.1–100.0 mg. per dose or 5 ml. portion of liquid in a pharmaceutically acceptable vehicle, said composition being comparable in efficacy to compositions containing capsaicin but with significantly less local adverse effects normally associated with capsaicin.

14. The method of claim 13 wherein said cis-8-methyl-N-vanillyl-6-nonenamide is present in the amount of about 0.5–50.0 mg per dose.

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United States Patent [19]
Bernstein

[11] Patent Number: 4,588,590
[45] Date of Patent: May 13, 1986

[54] METHOD OF TREATING KERATOSIS AND COMPOSITIONS USEFUL THEREFOR

[75] Inventor: Joel E. Bernstein, Deerfield, Ill.

[73] Assignee: Jaye-Boern Laboratories, Inc., Northbrook, Ill.

[21] Appl. No.: 572,899

[22] Filed: Jan. 23, 1984

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 332,676, Dec. 21, 1981, abandoned.

[51] Int. Cl.[4] A61K 35/78; A61K 7/04; A61K 31/60; A61K 31/19

[52] U.S. Cl. 424/195.1; 424/61; 514/159; 514/474; 514/557; 514/563

[58] Field of Search 424/145, 61, 230, 317, 424/195.1; 514/159, 474, 557, 563

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Primary Examiner—Albert T. Meyers
Assistant Examiner—Freda Abramson
Attorney, Agent, or Firm—Ronald A. Sandler; Jerry A. Schulman; Timothy T. Patula

[57] ABSTRACT

The present invention includes an improved method of treating keratosis comprising periodically applying to the affected area a nail polish composition containing an effective amount of at least one corrosive agent for relieving the keratosis; also nail polish compositions are disclosed for use in the method.

11 Claims, No Drawings

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METHOD OF TREATING KERATOSIS AND COMPOSITIONS USEFUL THEREFOR

BACKGROUND OF THE INVENTION

This is a continuation-in-part of application Ser. No. 332,676, filed Dec. 21, 1981, since abandoned.

This invention generally relates to an improved method of treating keratosis and is particularly directed to novel nail polish compositions for use in such improved method.

Keratosis is generally used to describe any disease of the skin characterized by an overgrowth of the epithelium. In particular, these diseases include what are commonly referred to as warts, corns and calluses. Warts are small intraepidermal growths of the skin caused by human papilloma virus and appear in children and young adults on the hands, face and feet. Corns are sharply demarcated hyperkeratotic lesions with a central core which are observed almost exclusively on the feet. Calluses are also hyperkeratotic lesions but have no central core and have a more diffuse outline. Calluses appear on the feet and hands where they may cause pain and discomfort.

Treatment of keratosis includes the use of drugs with sufficient corrosive activity so as to cause peeling of the hyperkeratotic lesion. Topical corrosive agents used in the treatment of keratosis incude ascorbic acid, glacial acetic acid, lactic acid, salicylic acid, trichloroacetic acid. calcium pantothenate, zinc chloride, and podophyllum resin.

The corrosive agents are generally formulated in flexible collodion vehicles or volatile solvents such as ether or alcohol. Although the collodion vehicles and solvents used in the prior art moderately reduce moisture exchange between the skin and the environment, they are not completely occlusive. It is desirable to form a completely occlusive film over the keratotic area to prevent moisture exchange between the skin and the environment, and thus increase the activity of the corrosive agent. Furthermore, the collodion vehicles and solvents used heretofore deteriorate rapidly, requiring several applications per day in order to expose the keratotic condition to the corrosive agent for a sufficient length of time.

The use of nail polish as a vehicle for applying topical steriods to nails is disclosed in U.S. patent application Ser. No. 28,092, for "A Method for Treating Psoriasis of the Nails and Composition". The nail polish compositions disclosed therein induce a soothing, anti-inflammatory effect on the nails affected by psoriasis. By contrast, the nail polish compositions of the present invention produce an occlusion having a corrosive, inflammatory and irritating effect on the skin.

SUMMARY OF THE DISCLOSURE

It is an object of the invention to provide an improved method of treating keratosis with a nail polish composition which reduces the moisture exchange between the skin and the environment.

It is a further object of the invention to provde a nail polish composition which increases the activity of the corrosive agent incorporated in the composition.

A still further object of the invention is to provide a nail polish composition which covers the area of the skin affected by keratosis for more than a day, before deterioration of the composition requires reapplication.

Another object of the invention is to provide a method for relieving keratosis which is easy, convenient, and simple for children or adults to use.

Still another object of the invention is to provide a nail polish composition for relieving keratosis which is relatively inexpensive and generally affordable by the public.

Keratosis is treated by periodically applying to the affected area a nail polish composition containing an effective amount of at least one corrosive agent for relieving the keratosis.

For a better understanding of the present invention, together with other and further objects thereof, references are made to the following description, taken in connection with the accompanying examples. The scope of the invention will be pointed out in the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the practice of the present invention, at least one corrosive agent is incorporated into a nail polish vehicle which is applied over the area affected by keratosis. The application of the nail polish composition is a simple covering of the affected area by brushing, smearing, or painting. The composition dries quickly to form a fairly durable cover.

The present invention contemplates the use of a corrosive agent which gradually wears away the keratotic lesion by chemical action. A suitable corrosive agent is identified by its corrosive, inflammatory, and irritating action on the affected area of the skin. The corrosive agent must also be non-toxic and otherwise pharmaceutically acceptable. Exemplary corrosive agents include acids, in particular, those carboxylic acids which are pharmaceutically acceptable. In particular, the following chemicals are known corrosive agents and are preferred for use in the invention: ascorbic acid, glacial acetic acid, lactic acid, salicylic acid, trichloroacetic acid, calcium pantothenate, zinc chloride, and podophyllum resin. The present invention contemplate the use of other known corrosive agents as well.

The corrosive agent incorporated in the nail polish composition is present in an amount effective to relieve the keratotic condition with periodic application. More than one corrosive agent may be included in the nail polish composition. Preferably, each corrosive agent is present in an amount between about 5% and 40% of the total weight of the composition. A more preferred range for each corrosive agent in the composition is an amount between about 5% and 20% of the total weight.

The present invention contemplates the use of any commercial nail polish, colored or clear, as a vehicle for the corrosive agent. It is critical, however, that the selected nail polish form an occlusion over the affected area when dry. Although nail polishes manufactured under the trade names Revlon and Cutex are used in the examples below, these nail polishes are for illustrative purposes only and are not intended as a limitation.

Having described the invention in general terms, the following examples are set forth to more fully illustrate the preferred embodiments of the invention. These examples, however, are not meant to be limiting. It is possible to produce still other embodiments without departing from the inventive concept herein disclosed. Such embodiments are within the ability of one skilled in the art.

EXAMPLE 1

A nail polish composition useful in treating keratosis was prepared by mixing salicylic acid with Revlon clear nail polish in the amount of 1% by total weight and painting a wart on the foot of an 11 year old boy every 48 hours for 3 weeks with the composition. Unexpectedly, all signs of the wart disappeared with this treatment regimen.

EXAMPLE 2

A nail polish composition was prepared by mixing salicylic acid in Cutex clear nail polish in the amount of 5% by weight. The composition was applied to 5 warts on the hands of a 7 year old girl once daily for 2 weeks. Once again, the warts flattened and disappeared over this period with only one wart requiring freezing of the base.

EXAMPLE 3

A nail polish composition was prepared by mixing salicylic acid in Revlon clear nail polish in the amount of 20% by weight and the resulting composition was applied to a corn on the lateral surface of the left foot of a 37 year old woman. Unanticipated results were obtained. With similar applications made every 48 hours for 2 weeks, the corn totally disappeared.

EXAMPLE 4

A nail polish composition was prepared by mixing lactic acid into Revlon clear nail polish in the amount of 10% by weight and the resulting composition was applied once daily to a wart one cm in diameter on the right hand of a 10 year old boy. A wart of the same size on the left hand was treated similarly with a daily application of a second nail polish composition which incorporated by weight 16% lactic acid and 16% salicylic acid in Revlon clear nail polish. After two weeks of treatment, the wart on the right hand disappeared and although the wart on the left hand nearly disappeared, some traces of the wart still remained which required additional treatment before disappearing completely.

EXAMPLE 5

A nail polish composition was prepared by mixing lactic acid in Cutex clear nail polish in the amount of 5% by weight and the resulting composition was applied 3 times weekly to a callus on the sole of the foot of a 38 year old male. Unforeseen, the callus disappeared within 10 days.

EXAMPLE 6

A nail polish composition was prepared by mixing glacial acetic acid in Revlon clear nail polish in the amount of 5% by weight and the resulting composition was applied once daily to 8 warts on the hands and elbows of a 24 year old female. Wholly unexpected results were obtained. Within 3 weeks, no trace of the warts remained.

EXAMPLE 7

A nail polish composition was prepared by incorporating by weight 10% lactic acid and 10% salicylic acid in Revlon clear nail polish and the resulting composition was applied every other day to a large plantars wart on the sole of an 11 year old boy. After 21 days of such therapy, the wart was nearly disappeared. After freezing the base, the plantars wart never recurred.

EXAMPLE 8

A nail polish composition was prepared by mixing 15% lactic and 15% glacial acetic acid by weight in Revlon clear nail polish. The composition was applied once daily to calluses on the palms of a 38 year old man. After 1 week of such treatment the calluses disappeared.

EXAMPLE 9

A nail polish composition was prepared by mixing 5% salicylic acid, 5% lactic acid and 5% glacial acetic acid by weight in Cutex clear nail polish and the resulting composition was applied once every 48 to 72 hours to a corn on the big toe of a 30 year old female. Unexpectedly, the corn disappeared after 2 weeks of treatment.

EXAMPLE 10

A nail polish composition was prepared by mixing 20% lactic acid and 20% glacial acetic acid by weight in Revlon clear nail polish and the resulting composition was applied once every 3 days to a wart on the dorsum of the right hand of a 13 year old girl. Although the skin surrounding the wart became mildly irritated, the wart disappeared within 2 weeks of treatment.

As demonstrated by these examples, this invention provides an improved method and composition for treating keratosis. The occlusion formed by the nail polish composition over the affected area reduces the moisture exchange between the skin and the environment. The durability of the nail polish composition covering the affected area allows for prolonged contact with the corrosive agent. For these reasons, the activity of the corrosive agent on the keratotic condition is increased, with fewer applications of the corrosive agent.

These examples also show that the present invention provides a method for relieving keratosis which is relatively painless, easy and convenient for both children and adults to use because of it simplicity. Furthermore, the invention is relatively inexpensive and would be affordable by the general public.

A small clinical study performed by Applicant compared the efficacy of varying concentrations of salicylic acid in a carrier for the purpose of treating warts. The results were as follows:

Concentration of Salicylic Acid	No. of Warts Treated	% Cured or Improved
1%	5	20%
5%	4	75%
17%	5	80%
Carrier Only	5	20%

Thus, preferred results have been achieved through use of keratolytic substances of the types discussed hereinabove in amounts ranging from about 5% to about 20% by weight with respect to the carrier.

While there has been described what is at present considered to be the preferred embodiments of the invention, it will be obvious to those skilled in the art that various changes and modifications may be made therein, without departing from the invention and that it is, therefore, the intent of the appended claims to cover all such changes and modifications as fall within the true spirit and scope of the invention.

Claim:

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I claim:

1. A method of treating warts, corns, and calluses comprising periodically applying to the affected area a nail polish composition containing an effective amount of at least one non-toxic and pharmaceutically acceptable corrosive agent sufficient to cause peeling of the wart, corn, or callus for relieving said warts, corns, or calluses.

2. A method as defined in claim 1, wherein each said corrosive agent is a pharmaceutically acceptable acid.

3. A method as defined in claim 1, wherein each said corrosive agent is a pharmaceutically acceptable carboxylic acid.

4. A method as defined in claim 1, wherein each said corrosive agent is selected from the group consisting of salicylic acid, lactic acid, glacial acetic acid, ascorbic acid, calcium pantothenate, podophyllum resin, and trichloroacetic acid.

5. A method as defined in claim 1, wherein the total concentration of said corrosive agent or agents is an amount between about at least 5% and 40% by weight.

6. A nail polish composition for relieving warts, corns and calluses comprising a nail polish vehicle containing an effective amount of at least one non-toxic and pharmaceutically acceptable corrosive agent, in a concentration of at least 5% by weight, sufficient to cause peeling of said warts, corns, and calluses.

7. A nail polish composition as defined in claim 6, wherein each said corrosive agent is a pharmaceutically acceptable acid.

8. A nail polish composition as defined in claim 6, wherein each said corrosive agent is a pharmaceutically acceptable carboxylic acid.

9. A nail polish composition as defined in claim 6, wherein each said corrosive agent is selected from the group consisting of salicylic acid, lactic acid, glacial acetic acid, ascorbic acid, calcium pantothenate, podophyllum resin, and trichloroacetic acid.

10. A nail polish composition as defined in claim 6, wherein the total concentration of said corrosive agent or agents is an amount between about at least 5% and 40% by weight.

11. A nail polish composition as defined in claim 6, wherein the total concentration of said corrosive agent or agents is an amount between about at least 5% and 20% by weight.

* * * * *

United States Patent [19]

Bernstein

[11] **4,416,886**

[45] **Nov. 22, 1983**

[54] **METHOD OF TREATING PRURITIS AND COMPOSITION THEREFOR**

[75] Inventor: **Joel E. Bernstein,** Deerfield, Ill.

[73] Assignee: **Dermall Limited,** Northbrook, Ill.

[21] Appl. No.: **288,166**

[22] Filed: **Jul. 29, 1981**

[51] **Int. Cl.**[3] **A61K 31/485**

[52] **U.S. Cl.** **424/260**

[58] **Field of Search** 424/260

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Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Emrich & Lee and Brown, Hill, Dithmar, Stotland, Stratman & Levy

[57] **ABSTRACT**

A topical treatment for relieving pruritis wherein naloxone, a pharmaceutically acceptable salt or a pharmaceutically acceptable chemical derivative is topically applied in a lotion, solution, cream or ointment.

9 Claims, No Drawings

METHOD OF TREATING PRURITIS AND COMPOSITION THEREFOR

BACKGROUND OF THE INVENTION

Itching or pruritis is a common dermatologic symptom. The causes of pruritis are complex and poorly understood. The best understood mechanism of itching is the release of histamine in the skin leading to urticarial wheals and intense itching. Such itching has traditionally been relieved by antihistamines. While antihistamine therapy is often effective, the sedation and drowsiness produced by antihistaminic agents limits their effectiveness.

Many kinds of itching are not however easily relieved by antihistamines. For example, conditions such as Hodgkin's Disease, mycosis fungoides (cutaneous malignacy) and severe jaundice produce intense itching unrelieved by antihistamines. Therefore, there is a need for improved treatment to relieve severe itching which can not only be an alternative to antihistaminic treatment of itching due to such causes as mosquitoe bites which responds to such treatment, but which further provides relief in intractable cases of pruritis which heretofore have been virtually impossible to treat except as disclosed in my prior U.S. Pat. No. 4,181,726 issued Jan. 1, 1980, a method based on the systemic effect on the central nervous system. The present invention provides such a composition and method independent of systemic effects on the central nervous system.

Naloxone is a narcotic antagonist which is not known to cause physical or psychological dependence and which exhibits essentially no pharmacological activity in non-addicts. Naloxone is normally given by injection to addicts to assist them in narcotic withdrawal and sometimes is administered to post operative patients for partial reversal of narcotic depression following the use of narcotics during surgery.

It has been found surprisingly that topical applications of naloxone are useful in alleviating severe itching in various conditions.

SUMMARY OF THE INVENTION

The present invention provides an improved composition and method of treating severe itching comprising topically administering a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable chemical derivative thereof to a mammalian patient in need of such treatment.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Naloxone hydrochloride is commercially available from Endo Laboratories, Inc., a subsidiary of the DuPont Company, 1000 Stewart Avenue, Garden City, N.Y. 11530. The preparation of naloxone is disclosed in U.S. Pat. No. 3,254,088.

The term pharmaceutically acceptable salts, as used herein, refers to the physiologically acceptable acid addition salts of naloxone such as the hydrochloride, hydrobromide, hydroiodide, acetate, valerate, oleate, etc.

Liquid dosage forms for topical administration includes acceptable emulsions, solutions and suspensions containing volatile diluents commonly used in the art, such as alcohol, glycol and the like. Besides such diluents, topically applied compositions may also include wetting agents, emulsifying and suspending agents.

In the practice of this invention naloxone in the form of a pharmaceutically acceptable salt such as the hydrochloride and pharmaceutically acceptable chemical derivatives thereof such as naltrexone which is the n-methyl cyclopropyl derivative are incororated into solutions, lotions, creams, and ointments for topical application in concentrations of from 0.01 to about 5 percent by weight. These topical products are applied to the skin 1 to 8 times daily. The relief experienced by those receiving the topical application was prompt although temporary.

EXAMPLE 1

1 percent by weight naloxone hydrochloride was incorporated into a solution composed of 70 percent by volume ethyl alcohol and 30 percent by volume propylene glycol and applied 6 times daily to 2 mosquito bites of less than 24 hours duration on a 11 year-old male. This child noted relief from his itching within 10 minutes of each application and the relief lasted 2–4 hours.

EXAMPLE 2

A 0.05% by weight naloxone hydrochloride was incorporated into Eucerin ® cream and applied 4 times daily to the body of a 60 year-old male with intractable itching due to mycosis fungoides. Eucerin ® cream is a synthetic lanolin containing cream produced by Beiersdorf, Inc. of South Norwalk, Conn. 06854. This was the first topical product the patient used that provided him with any significant relief from his itching.

EXAMPLE 3

An ointment composed chiefly of petrolatum and containing 0.01% by weight naloxone hydrochloride was applied 4 times daily to the body of a 60 year-old male with mycosis fungoides. Itching was diminished, although not as much as with the higher concentration of naloxone in Example 2.

EXAMPLE 4

0.1% by weight naloxone hydrochloride was incorporated into a zinc shake lotion and applied to the mosquitoe bites of a 6 year-old girl during a one month five interval in the summer. This lotion provided excellent relief from the itching.

EXAMPLE 5

5% by weight naloxone hydrochloride was incorporated into an ointment and applied 4 times daily for two days to a small eczematous patch on the left hand of a 38 year-old male. Itching was dramatically reduced by each application of the test ointment.

It will be apparent to those skilled in the art that only the preferred embodiments have been described by way of exemplification and that there are various modifications which fall within the scope of this invention.

I claim:

1. A method for relieving severe itching in patients in need of such treatment, said method comprising topically administering a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or naltrexone to a patient in need of such treatment.

2. The method of claim **1**, wherein said naloxone or pharmaceutically acceptable salt thereof or naltrexone is present in a solution, lotion, cream or ointment in the

range of between about .01 percent by weight to about 5 percent by weight.

3. The method of claim 1, wherein said naloxone or a pharmaceutically acceptable salt thereof or naltrexone is administered to a patient in need of such treatment periodically from 1 to 8 times per day.

4. The method of claim 1, wherein said pharmaceutically acceptable salt of naloxone is a physiologically acceptable acid addition salt.

5. The method of claim 1, wherein said pharmaceutically acceptable salt of naloxone is naloxone hydrochloride.

6. A composition of matter comprising a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof or naltrexone in a lotion, cream or ointment suitable for topical use only.

7. The composition of claim 6, wherein naloxone or a pharmaceutically acceptable salt thereof or naltrexone is present in the lotion, cream or ointment in the range of between about 0.01 percent by weight to about 5 percent by weight.

8. The composition of claim 6, wherein the pharmaceutically acceptable salt of naloxone is a physiologically acceptable acid addition salt.

9. The composition of claim 8, wherein said salt is naloxone hydrochloride.

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DIAMAR, SIDLEAND, SINAIMAN
100 N. WACKER DR. *SUITE 2000
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United States Patent [19]

Bernstein

[11] **4,395,420**

[45] **Jul. 26, 1983**

[54] **METHOD AND COMPOSITION FOR TREATING PRURITIS**

[76] Inventor: **Joel E. Bernstein,** 615 Brierhill Rd., Deerfield, Ill. 60015

[21] Appl. No.: **328,955**

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[51] **Int. Cl.**[3] **A61K 31/02;** A61K 31/33; A61K 31/135; A61K 31/335

[52] **U.S. Cl.** **424/278;** 424/244; 424/330; 424/350

[58] **Field of Search** 424/278

[56] **References Cited**

PUBLICATIONS

Merck Index 9th Ed. (1976) p. 456.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Emrich & Lee and Brown, Hill, Dithmar, Stotland, Stratman & Levy

[57] **ABSTRACT**

A method of and composition for treating pruritis comprising topically applying a therapeutically effective amount of a tricyclic anti-depressant in a pharmaceutically acceptable carrier. The tricyclic is present in the range of from about 0.1% to about 10% by weight of the carrier and is applied in divided doses.

16 Claims, No Drawings

METHOD AND COMPOSITION FOR TREATING PRURITIS

BACKGROUND OF THE INVENTION

Itching or pruritis is a common dermatologic symptom. The causes of pruritis are complex and poorly understood. The best understood mechanism of itching is the release of histamine in the skin leading to urticarial wheals and intense itching. Such itching has traditionally been relieved by antihistamines. While antihistamine therapy is often effective, the sedation and drowsiness produced by antihistaminic agents limits their effectiveness.

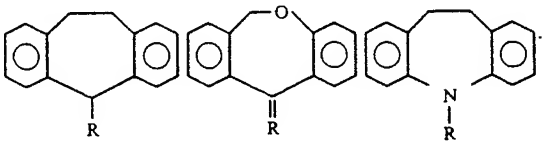
Many kinds of itching are not however easily relieved by antihistamines. For example, conditions such as Hodgkin's Disease, mycosis fungoides (cutaneous malignancy) and severe jaundice produce intense itching unrelieved by antihistamines. Therefore, there is a need for improved treatment to relieve itching which can not only be an alternative to antihistaminic treatment of itching due to such causes as mosquitoe bites which responds to such treatment, but which further provides relief in intractable cases of pruritis which heretofore have been virtually impossible to treat except as disclosed in my prior U.S. Pat. No. 4,181,726 issued Jan. 1, 1980, a method based on the systemic effect on the central nervous system. The present invention provides such a composition and method independent of systemic effects on the central nervous system.

I have discovered surprisingly that tricyclic antidepressants usually prescribed for ameliorating the effects of severe depression are effective at relieving itching when applied topically. These compounds include the pharmaceutically acceptable salts of the tricyclics. The term pharmaceutically acceptable salts, as used herein, refers to the physiologically acceptable acid addition salts such as the hydrochloride, hydrobromide, hydroiodide, acetate, valerate, oleate, etc. Doxepin, amitriptyline and imipramine respectively are the tertiary amine derivatives of dibenzoxepin, dibenzocycloheptadiene and dibenzazepine wherein the nitrogen atom is connected to the ring structure by a three carbon aliphatic chain and the tertiary amine has two carbon atoms attached thereto in addition to the aliphatic chain.

The present invention relates to a method and composition for topically treating pruritis.

A principal object of the present invention is topically to apply divided doses of tricyclic anti-depressant compounds traditionally employed systemically for treatment of mental depression to relieve pruritis.

Yet another object of the present invention is to provide a method and composition for treating pruritis wherein the tricyclic anti-depressant contains one of the following ring structures:



These and other objects of the present invention may be more readily understood when considered in conjunction with the following detailed description and examples.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I investigated the possible antipruritic effects of topically applied formulations containing doxepin hydrochloride, amitriptyline hydrochloride, and imipramine hydrochloride by incorporating such tricyclic antidepressant compounds into suitable dermatological vehicles and having patients with itchy skin disorders apply such formulations for relief. These topical formulations were surprisingly effective at alleviating many types of pruritis.

In the practice of this invention concentrations of salts of doxepin, amitriptyline and imipramine varying from 0.1% by weight to about 10% by weight, were incorporated into creams, ointments, lotions and solutions and applied to itchy skin in divided doses for the relief of such itching. The preferred amount of active ingredient is from about 0.5% by weight to about 5% by weight of the carrier.

EXAMPLE 1

A topical formulation prepared by incorporating one tenth percent (0.1%) by weight doxepin hydrochloride in unscented cold cream was applied twice daily over a two week period by a 73 year-old woman with moderate itching due to dry skin (xerosis or asteatrosis). The doxepin cream provided some, but not complete relief of the itching during the period of application.

EXAMPLE 2

A solution prepared by incorporating two percent (2%) by weight doxepin hydrochloride in 95% ethanol in water was applied to the mosquito bites of an eleven year-old male. Such applications provided prompt temporary relief of the itching associated with these bites.

EXAMPLE 3

Ten percent (10%) by weight doxepin hydrochloride was incorporated into white petrolatum and applied to the skin of a thirty-six year-old female patient with an itchy eczematous eruption on her arms. The doxepin cream produced dramatic relief of the itching but had to be discontinued after five days due to a possible irritation or sensitization reaction.

EXAMPLE 4

One percent (1%) by weight amitriptyline hydrochloride was incorporated in calamine lotion and applied to an itchy patch of skin on the hands and arms of a thirty-six year-old patient suffering from poison ivy dermatitis. The lotion produced excellent relief of the itching.

EXAMPLE 5

A cream was prepared by compounding five percent (5%) by weight amitriptyline hydrochloride in unscented cold cream and the resulting cream was applied to the itchy perianal area of a patient with pruritus ani. Relief was prompt and was maintained on a 4–5x/day application schedule.

EXAMPLE 6

A two percent (2%) by weight imipramine hydrochloride ointment, prepared by incorporating the active agent in white petrolatum, was applied to the body of a

seventy-two year-old male with generalized itching secondary to dry skin (xerosis or asteatosis). Application of this ointment twice daily provided excellent relief of the itching.

It will be apparent to those skilled in the art that only the preferred embodiments have been described by way of exemplification and that there are various modifications which fall within the scope of this invention.

What is claimed is:

1. A method of treating pruritis in humans in need of such treatment comprising topically applying a therapeutically effective amount of doxepin or a physiologically acceptable acid addition salt thereof.

2. The method of claim **1**, wherein the doxepin or acid addition salt thereof is present in a pharmaceutically acceptable carrier at a concentration of not less than about 0.1% by weight of the carrier.

3. The method of claim **1**, wherein the doxepin or the acid addition salt thereof is present in a pharmaceutically acceptable carrier at a concentration in the range of from about 0.1% by weight to about 10% by weight of the carrier.

4. The method of claim **1**, wherein the doxepin or the acid addition salt thereof is present in a pharmaceutically acceptable carrier at a concentration in the range of from about 0.5% by weight to about 5% by weight of the carrier.

5. The method of claim **1**, wherein the acid addition salt is selected from the class consisting of halides other than fluoride, acetate, valerate, and oleate.

6. The method of claim **5**, wherein the acid addition salt is doxepin hydrochloride and is present in the range of from 0.5% by weight to about 10% by weight of the carrier.

7. The method of claim **1**, wherein the carrier is an ointment or cream.

8. The method of claim **1**, wherein the carrier is an aqueous-alcohol solution.

9. A composition for treating pruritis comprising a carrier pharmaceutically acceptable for topical application to the skin containing a therapeutic amount of doxepin or a physiologically acceptable acid addition salt thereof.

10. The composition of claim **9**, wherein the doxepin or acid addition salt thereof is present in the carrier at a concentration of not less than about 0.1% by weight of the carrier.

11. The composition of claim **9**, wherein the doxepin or acid addition salt thereof is present in the carrier at a concentration in the range of between about 0.1% by weight and about 10% by weight of the carrier.

12. The composition of claim **9**, wherein the doxepin or acid addition salt thereof is present in a pharmaceutically acceptable carrier at a concentration in the range of from about 0.5% by weight to about 5% by weight of the carrier.

13. The composiition of claim **9**, wherein the acid addition salt is selected from the class consisting of halides other than fluoride, acetate, valerate, and oleate.

14. The composition of claim **13**, wherein the acid addition salt is doxepin hydrochloride and is present in the range of from 0.5% by weight to about 10% by weight of the carrier.

15. The composition of claim **9**, wherein the carrier is an ointment or cream.

16. The composition of claim **9**, wherein the carrier is an aqueous-alcohol solution.

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